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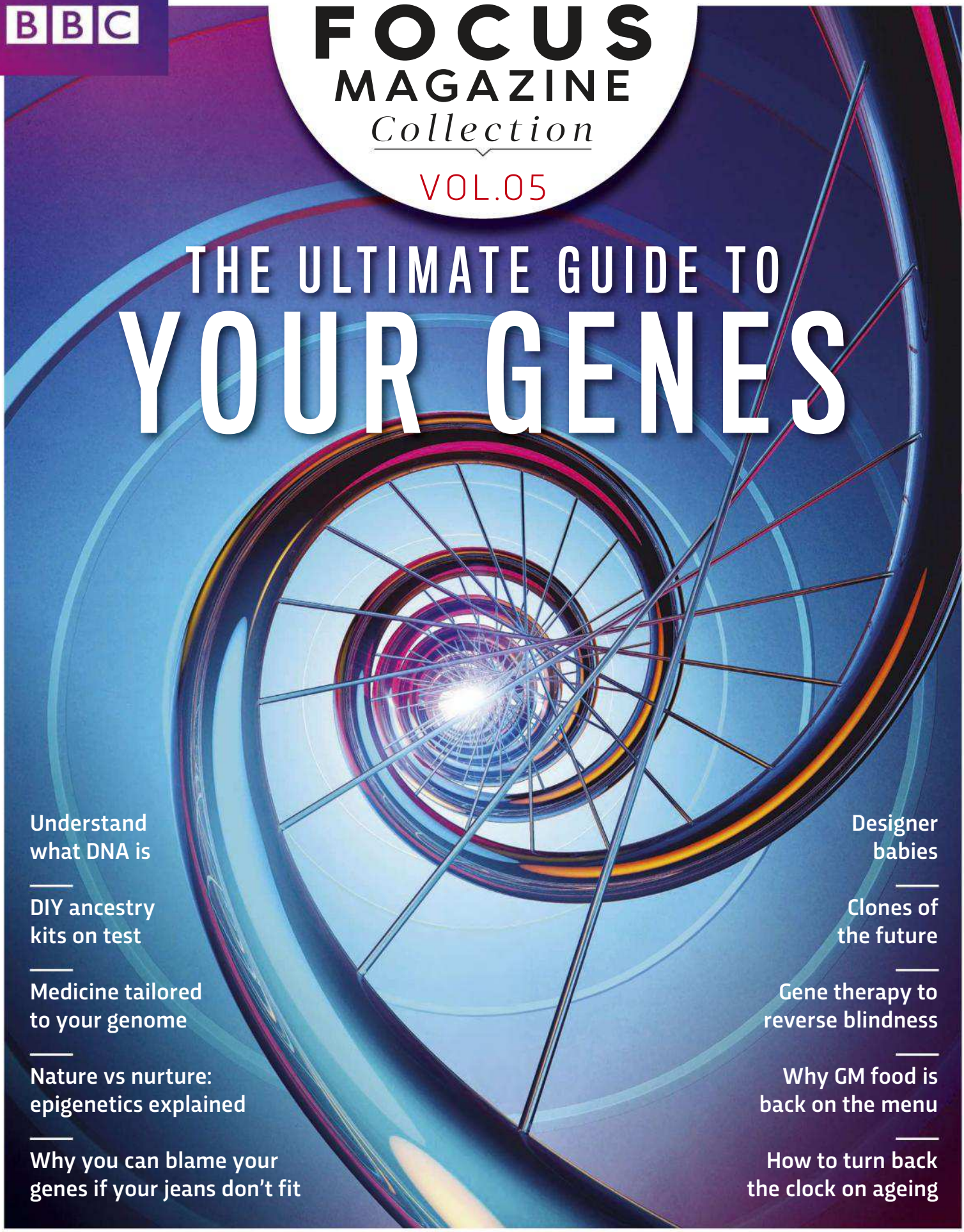
THE ULTIMATE GUIDE TO YOUR GENES



Understand what DNA is

DIY ancestry kits on test

Medicine tailored to your genome

Nature vs nurture: epigenetics explained

Why you can blame your genes if your jeans don't fit

Designer babies

Clones of the future

Gene therapy to reverse blindness

Why GM food is back on the menu

How to turn back the clock on ageing

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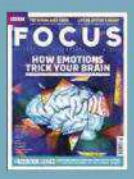

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The code to life

In 1953, two biochemists James Watson and Francis Crick, walked into a pub in Cambridge and declared: "We have discovered the secret of life!" They weren't exaggerating. They had worked out the structure of DNA and, with it, unlocked many of the mysteries of how living things make and replicate themselves.

They owed their discovery in part to the work of Rosalind Franklin and her PhD student Raymond Gosling, who took the now famous 'Photo 51', which showed the pattern formed by passing X-rays through a sample of DNA. By studying this image, Watson and Crick deduced the double helix structure of DNA.

This saga is just one of the many instances throughout history where breakthroughs have only been possible by building on the discoveries of others – as Newton so aptly put it, "If I have seen further, it is by standing upon the shoulders of giants". And that is the case for the field of genetics – discovering the structure of DNA eventually enabled the human genome to be decoded and creatures like Dolly the sheep to be cloned.

This special issue starts by looking at the basics of genetics, explaining all those terms that you might have heard of but maybe don't know exactly what they mean – DNA, genes, chromosomes, base pairs, nucleotides, epigenetics... We then focus on your health and how new discoveries in genetics are enabling breakthroughs, such as gene therapy to cure blindness and treatments to battle ageing, as well as discussing the new era of medicines tailored specially to your genome. Finally, we look at the future of genetics from cloning to genetic modification. Reading this special issue will help you understand more about what makes you 'you' and what the future holds for us and other creatures on this planet.

Daniel Bennett, Editor

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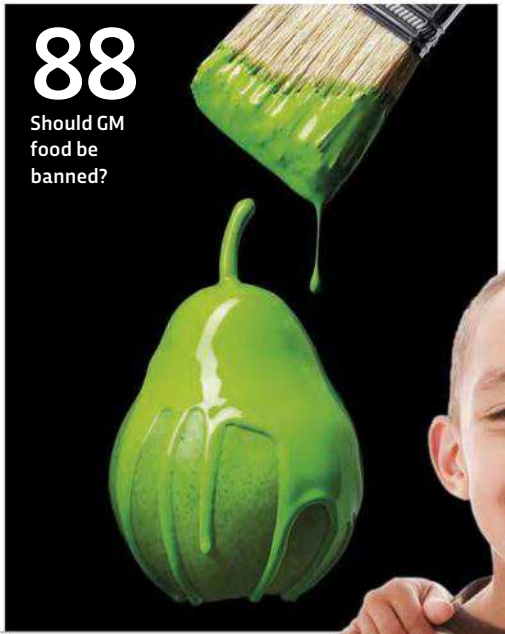

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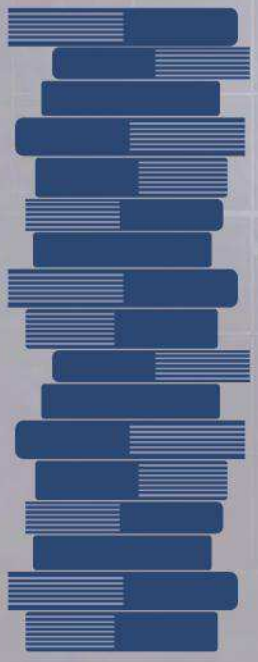
We share about 70% of our genes with acorn worms, which look nothing like us – they have no limbs and breathe through slits in their guts

The single-celled ***Amoeba dubia*** has one of the largest known genomes, containing 670 billion base pairs – over 200 times more than the human genome at 3.2 billion

UNLIKE GENES, CHROMOSOMES CAN BE SEEN UNDER A MICROSCOPE

Only about 2% of our DNA actually codes for genes. The rest is non-coding DNA

WE SHARE 99% OF OUR GENES WITH CHIMPANZEES



EACH OF US HAS ENOUGH DNA TO REACH FROM HERE TO THE SUN AND BACK, MORE THAN 300 TIMES

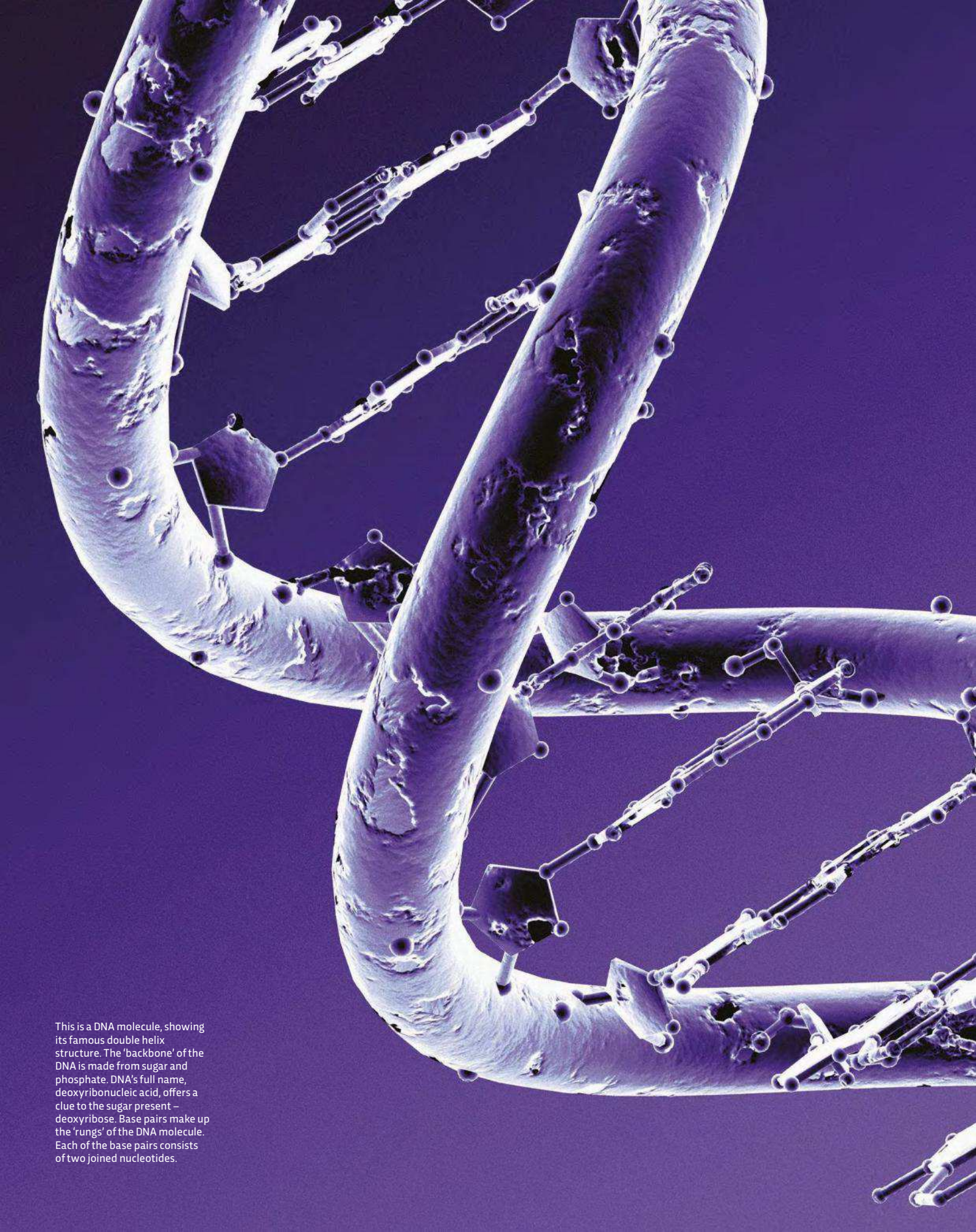
*If the 3.2 billion letters (bases) in your genome were printed out, they would fill a stack of paperback books **61 metres high***

THE FIRST DRAFT OF THE HUMAN GENOME WAS PUBLISHED IN 2003

GETTY

YOUR GENES

You are not like anyone else.
You share genetic material with every other human on the planet and have inherited specific genetic traits from your parents, but the particular combinations, omissions and duplications in your genetic code are unique to you and you alone. There is literally nobody else like you... Unless you're an identical twin. But even then you're only identical to begin with.

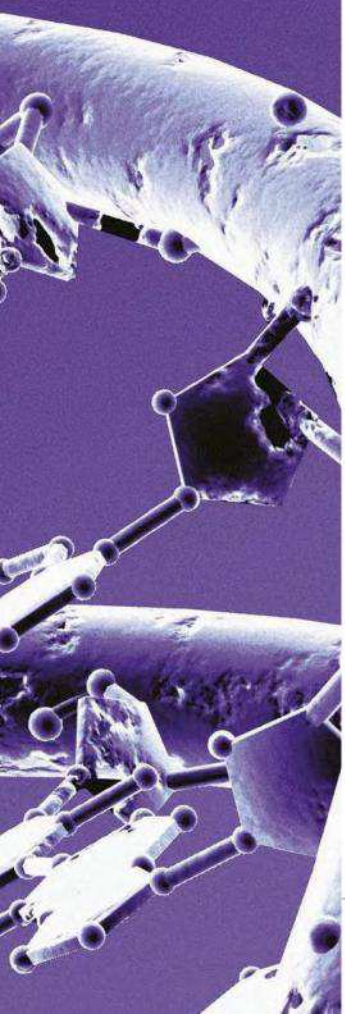


This is a DNA molecule, showing its famous double helix structure. The 'backbone' of the DNA is made from sugar and phosphate. DNA's full name, deoxyribonucleic acid, offers a clue to the sugar present – deoxyribose. Base pairs make up the 'rungs' of the DNA molecule. Each of the base pairs consists of two joined nucleotides.

DNA

We established DNA's structure in the 1950s. Since then, we've cloned animals and mapped the human genome. Here's everything you need to know about the complex molecule that is key to understanding life

WORDS: **TOM IRELAND**



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WHAT IS DNA?

Deoxyribonucleic acid is found at the heart of almost every living cell. It carries all of the instructions for an organism to build, maintain and repair itself. By replicating and passing on their DNA, animals, plants and microorganisms can impart their characteristics to their offspring.

In humans, half the DNA in our cells stems from our mother and half from our father. This is why we inherit a mixture of characteristics. DNA is a hugely long and complex code, and everyone's is unique. This 'genetic code' can tell us many things, such as details about ancestry and potential health problems.

Our understanding of DNA has revolutionised the whole of biology. It has allowed scientists to measure how closely organisms are related to one other, helping to both confirm and refine Charles Darwin's theory of evolution.

HOW DOES DNA WORK?

Establishing the structure of the DNA molecule was key to figuring out how it worked. Before that, scientists had no idea how this dense, stringy substance controlled qualities as diverse as human hair colour, or the shape of a bird's beak.

In 1953, biochemists James Watson and Francis Crick discovered that a DNA molecule is arranged like a very long, twisted ladder in a structure we call a double helix. Each 'rung' of the ladder is made up of a base pair – two joined chemical building blocks called nucleotides. There are four different types of these nucleotides: adenine, cytosine, guanine and thymine. We call these A, C, G and T. An A nucleotide always links to a T, while a C always links to a G. The exact order that the letters are arranged on the ladder varies, forming an enormously long code. Human DNA has about three billion 'rungs on the ladder'.

With modern technology we can extract DNA from cells and decipher the exact order of the base pairs, giving us an extraordinarily long string of letters A, C, T and G. This complex code will be different for every person and every organism (apart from identical twins), and is known as our DNA sequence or genome.

To understand how DNA works, we must

first understand proteins. Protein molecules perform many of the different tasks inside our cells, and help create many of the intricate structures within the body.

There are many different types of protein, but they are all made from long chains of chemical building blocks called amino acids.

The genetic code formed by DNA is like a language, which tells cells how to build the proteins they need. Different three-letter combinations in the DNA represent different types of amino acid – for example, the sequence 'GCA' is the code for an amino acid called alanine, and 'TGT' represents one called cysteine.

Molecular machinery within the cell 'scans' the DNA sequence of a gene. Every three letters, it adds the corresponding amino acid to a chain. There are even sections of DNA that mean 'stop' – the protein is finished.

Different combinations of amino acids create proteins with vastly different functions – from tiny chemical messengers like hormones to the tough, important molecules that form hair, skin and muscle. Proteins can also act as catalysts for important chemical reactions, or can create mini-machines that perform very specific tasks within cells.

There are hundreds of thousands of different proteins in the human body and many, many millions more throughout the natural world.

A scientist carrying out DNA sequencing to determine the order of the base pairs – the chemical building blocks called nucleotides

Variation in our genes causes variation in the proteins our cells produce, which in turn leads to differences in characteristics.

WHAT ARE GENES?

Genes are sections of our DNA sequence that contain the code for a specific protein, normally linked to a specific function or physical characteristic. In humans, for example, a stretch of DNA known as 'OCA2' has a strong influence on a person's eye colour. Variations in these parts of our DNA lead to the different characteristics we see among individuals. For example, people with blue eyes have different DNA at 'OCA2' than people with brown eyes.

A common misconception about genes is that one gene is responsible for one trait, which is actually highly unusual. More commonly, physical traits result from a combination of many genes. Scientists can study what a gene does by removing it or changing the sequence of base pairs, normally using animals like fruit flies, worms or mice. These 'mutant' animals are then studied to see what is different.

HOW DOES DNA REPLICATE?

The discovery of DNA's 'double helix' structure helped reveal the beautifully simple way a DNA molecule replicates itself. With the help of other chemicals in the cell, the double helix

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JARGON BUSTER

BASE PAIRS
DNA consists of building blocks called nucleotides. There are four different types and each is assigned a letter: A, C, G or T. A links with T and C links with G. When connected, these form the base pairs.

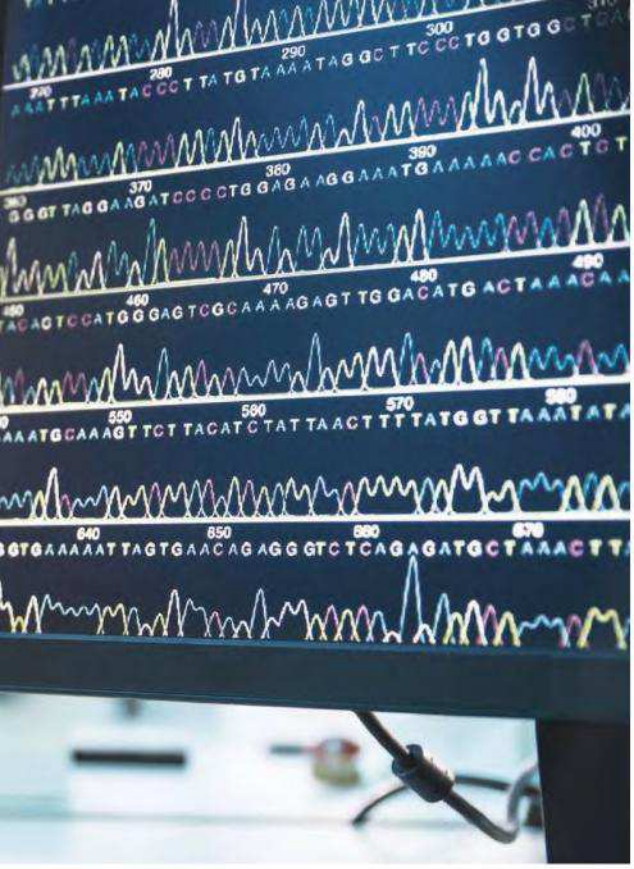
DNA SEQUENCING
This technique allows scientists to 'read' the sequence of nucleotides.

GENE
A section of DNA that has a particular function. Genes rarely do just one thing and often it is the combination of many genes that result in a physical characteristic like eye colour or height. You inherit genes from both your mother and your father.

GENOME
This is the entire DNA sequence of an organism. The human genome was sequenced in 2003. Everyone's genome is unique, but we can tell if we're closely related by studying similarities between genomes.

GENETIC DISORDER
A problem caused by one or more abnormalities in a person's genome, normally present from birth. Most genetic disorders are quite rare.

GENETIC MODIFICATION
Changing the DNA of an organism so that it has different properties, like inserting a gene from one crop into another to make it resistant to pests.



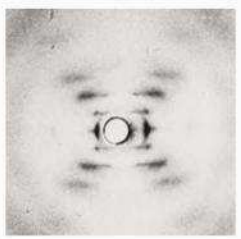
untwists and the two strands split down the middle, like a zip. Because A always pairs with T, and C with G, both strands then form an exact copy as more nucleotides are attracted into the corresponding place opposite the freshly split strands.

This replication process is important, because cells are constantly dividing and replicating. If DNA is copied incorrectly, the resulting cells have jumbled instructions and can start growing out of control. This is often how a cancerous tumour starts.

WHAT ARE CHROMOSOMES?

In animals and plants, the amount of DNA in each cell is so vast that it must be cleverly packaged into x-shaped bundles called chromosomes. These structures coil and fold the DNA so it doesn't take up too much room, while still allowing the cell to access all the important parts of the code. If it weren't wrapped up in chromosomes, scientists think the DNA in one human cell could stretch for more than 1.5m.

In humans, our entire genetic code is spread across 23 chromosomes. We each inherit one set of 23 from our mum, and another set of 23 from our dad, so each cell contains

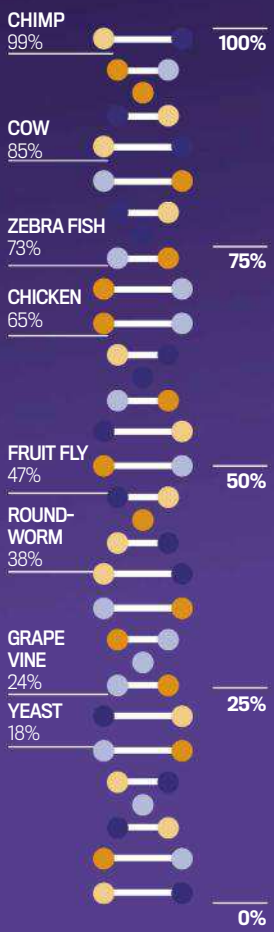


KEY EVIDENCE

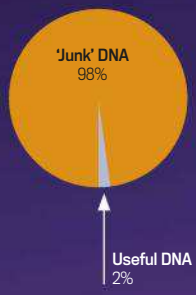
Above is 'Photo 51'. The image was made in 1952 by Raymond Gosling, a PhD student who was working under the supervision of the English chemist Rosalind Franklin (pictured below). The pattern formed by passing X-rays through a sample of DNA. One year later, Photo 51 helped Francis Crick and James Watson to figure out the double helix structure of DNA. The two scientists, along with Maurice Wilkins, were awarded Nobel Prizes for their discovery in 1962. Franklin died of cancer in 1958, aged 37.

DNA IN NUMBERS

AMOUNT OF DNA WE SHARE WITH OTHER SPECIES

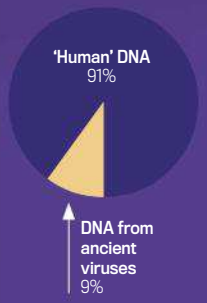


JUNK DNA



Up to 98 per cent of our DNA is 'non-coding' – meaning there are no genes in these sections

VIRUS DNA



Up to 9 per cent of our DNA is thought to be from ancient viruses that have merged with our genome (see page 22)

CAPACITY OF DNA

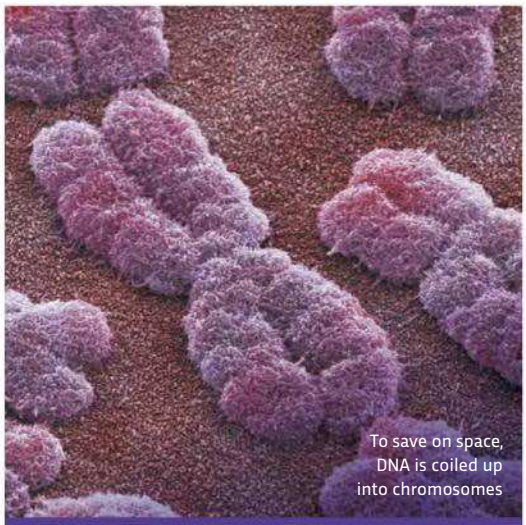
500,000

DVDs' worth of information can be stored in a **single gram of DNA**

SMALLEST GENOME

112,000

nucleotides are present in the bacteria *Nasuia deltocephalinicola* – the smallest genome found so far



To save on space, DNA is coiled up into chromosomes

EXPLAIN IT TO A FRIEND

1. YOUR DNA IS UNIQUE
DNA is a very long molecule that contains the instructions for living things to build and maintain themselves. All organisms have their own unique strands of DNA in each cell, which forms a very long code known as their genome.

2. CELLS READ THE GENES
Certain stretches of an organism's genome do certain things. These sections are called genes. Each cell can 'read' the code written in the genes and use it to build all the chemicals it needs.

3. DNA EXISTS IN CHROMOSOMES
Within each cell, DNA is kept in packages called chromosomes. We inherit 23 chromosomes from our mother and 23 from our father. Which ones our parents pass on to us determines many things, including what we look like, what diseases we are likely to get and even some aspects of our personality and behaviour.

SCIENCE PHOTO LIBRARY X3, GETTY X5, PRESS ASSOCIATION, KCL ARCHIVE

46 chromosomes. When people are born with too many or too few chromosomes, it can cause health issues. (For instance, people with Down's syndrome have three lots of chromosome 21 instead of a pair.) The sex chromosomes are different. One is called X and one is called Y. Males have one copy of each, X and Y, whereas females have two copies of X. When a sperm fuses with an egg, the new cell gets one of every chromosome from each parent. So it will have 23 pairs or 46 chromosomes, with either two X chromosomes (female) or one X and one Y (male). Different organisms have different numbers of genes and chromosomes in their cells. Mosquitoes have just six chromosomes, while a type of fern known as 'adder's tongue' has over 1,000.

A small number of genes have been linked to certain character traits, such as high intelligence or extreme anti-social behaviour, but the evidence is limited. It is more likely that lots of genes work in combination to influence our personality, and the experiences and events of our lives also shape the way our brains work.

Although every person's DNA sequence is unique, huge sections of it are identical between people and even animals. About 95 per cent of our genome is the same as a chimpanzee's, while 25 per cent is the same as a grape's.

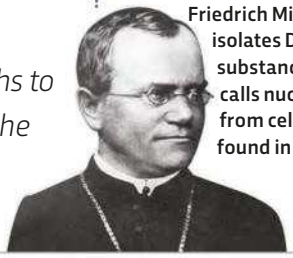
The amount of genetic variation between individual people is very small – just 0.1 per cent of the three billion base pairs will be different if you compare two people. Yet this variation gives rise to seemingly infinite appearances. To complicate matters further, the relatively new

Red blood cells do not contain DNA, so forensics have to extract DNA from white blood cells

TIMELINE

The discovery of DNA and its structure has enabled key breakthroughs to understand the code to life

1860s
Gregor Mendel establishes the basic rules of inheritance.



Friedrich Miescher isolates DNA, a substance he calls nuclein, from cells found in pus.

1944
Oswald Avery, Colin MacLeod and Maclyn McCarty demonstrate that DNA is the material which controls inheritance.

1952
PhD student Raymond Gosling (pictured) working under chemist Rosalind Franklin captures 'Photo 51' – the image used to work out DNA's structure.

1953
James Watson (left) and Francis Crick describe the structure of DNA, for which they were awarded a Nobel Prize.

field of 'epigenetics' is increasingly showing that our genes can be expressed differently – turned on and off – at different times throughout our lives, meaning the way our genes work is even more complex than we first thought. See page 14.

DOES DNA ENABLE EVOLUTION?

The fact that DNA can replicate itself is central to the evolution of all life on Earth. When early organisms replicated themselves, imperfections in the DNA copying process created new life with variations in their genetic code, leading to different features and characteristics in each generation.

Any characteristics that gave an advantage to the organism were more likely to survive and be passed on. Organisms that were hindered by their variations would be more likely to die or not reproduce.

Over generations, the successful DNA sequences flourished and replicated, while the not-so-good DNA sequences were consigned to the evolutionary dustbin.

Life on Earth became increasingly varied and complex, with the most successful variants in each generation passing their genes on to the next. Charles Darwin described this as 'natural selection', long before DNA was discovered.

Successful DNA replicated while not-so-good sequences went in the evolutionary dustbin

WHAT CAN WE DO WITH DNA?

We already use DNA for all sorts of useful applications that can tell us about our past, present and future: what our ancestors were like, what medicines we should take or avoid, and what illnesses we may develop. We can also use it to settle paternity disputes, or catch criminals, by searching for tiny amounts of DNA found at a crime scene.

But that's just the start. As DNA sequencing becomes vastly easier and cheaper, what once seemed unthinkable is now possible. Scientists can personalise medicines that are tailored to work with your exact combination of genes (see page 66). They are reading the genomes of cancer cells in order to fight them. And gene therapy can be used to combat genetic disorders.

In the future, biologists may create entirely new organisms to produce useful products for us. We may even be able to edit our offspring's genome – to guarantee they are free from genetic disorders, but also ensure they have the characteristics we want. Decoding DNA has unlocked the secrets of life.

Tom Ireland is a science journalist and managing editor at the Society of Biology.

1972

DNA from two different organisms is spliced together for the first time by Paul Berg, paving the way for genetic modification and the advent of GM foods.

1996

Dolly (pictured with her lambs) is born. Dolly is the first mammal cloned from a non-embryonic cell. Her DNA is identical to the sheep she was cloned from.

2003

After £3bn and 13 years of work, work on the Human Genome Project finishes and the entire genome of a human being is published.

2015

President Barack Obama announces plans to sequence the genomes of one million US citizens to help personalise medicine and learn more about rare diseases.

BBC RADIO 4

Listen to *DNA's Third Man* to find out about Maurice Wilkins *bbc.in/1BMtHLe*

The discovery that diet, lifestyle and the environment affect your genes radically changed our understanding of genetics and evolution

WORDS: **NESSA CAREY**

NATURE VS

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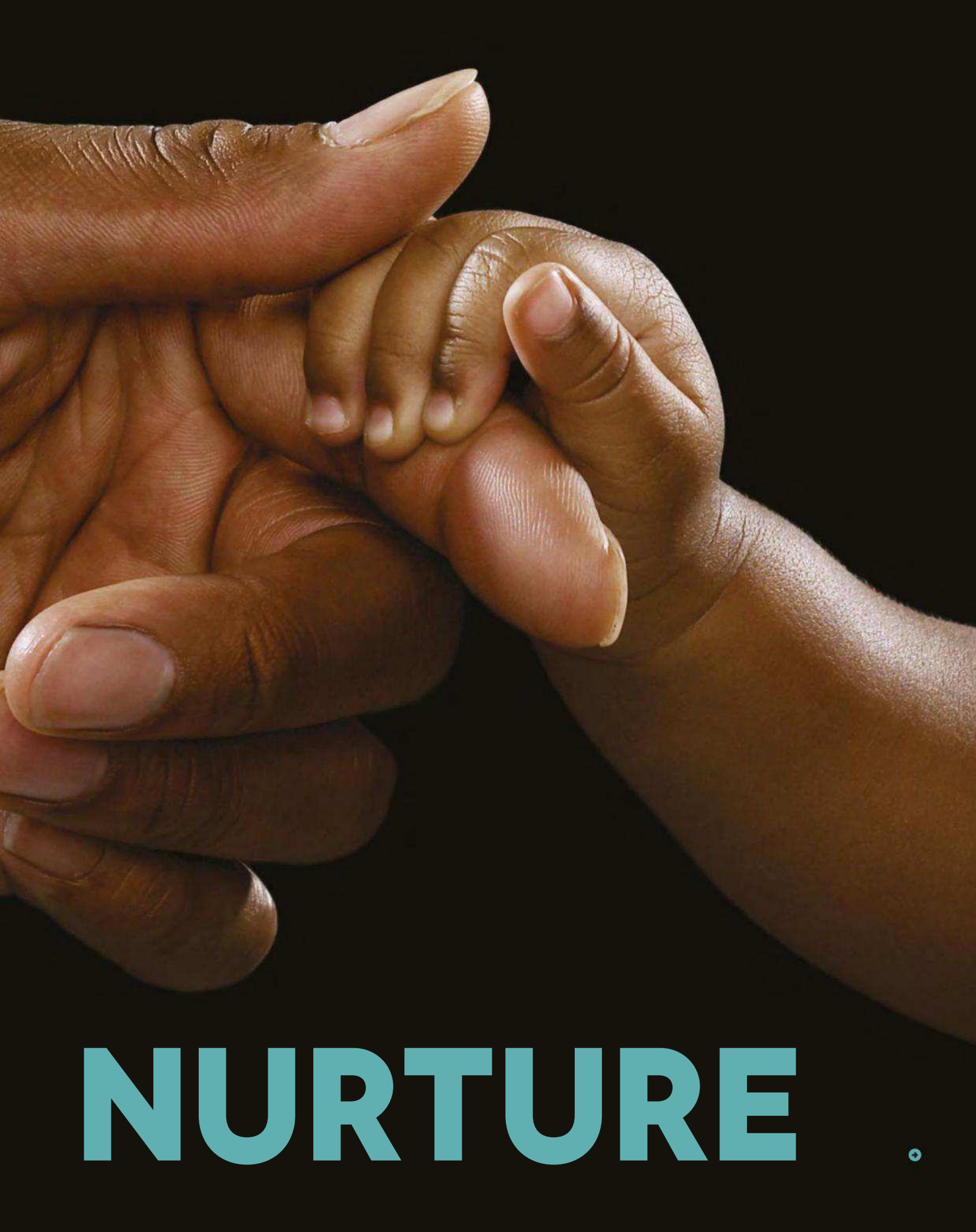


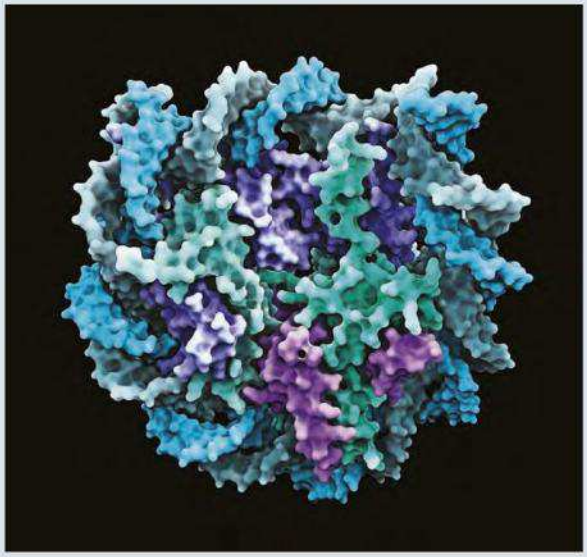
NURTURE

Epigenetic modifications change in response to environmental stimuli, and allow our cells to adapt their expression of particular genes to a change in circumstance

When Crick and Watson discovered the structure of DNA in 1953, we understood how attributes are passed on from one generation to the next. But DNA wasn't the whole of the story. Since the 1970s, the role of the 'epigenome' has come under ever greater scrutiny. The epigenome is the name given to tiny chemical modifications made by factors such as environment and diet to DNA and the proteins it wraps around. And studying these modifications has thrown up some surprising results. While your green eyes or dark skin are due to the DNA you inherited from your mother, your wiry build could have something to do with how your grandmother was living while she was carrying her.

The extraordinary process of development starts with a single cell with limitless potential and ends, in humans, with trillions of cells that have become specialised. Several decades ago, no one knew what happened to the DNA when cells became specialised. One hypothesis was that cells got rid of the DNA they no longer needed. For example, brain cells would 'lose' genes that code for haemoglobin, the pigment that carries oxygen in the blood, while liver cells would abandon DNA coding for keratin.

In the 1970s, Prof John Gurdon, working first in Oxford and subsequently in Cambridge, disproved this theory. He removed the nuclei from frogspawn and replaced them with the nuclei from adult frog cells. The frogspawn developed into tadpoles and finally frogs. This demonstrated that there is no difference in the DNA of different cells from an individual. In 1996, Ian Wilmut, Keith Campbell and colleagues at the Roslin Institute proved that the same is true in mammals when they



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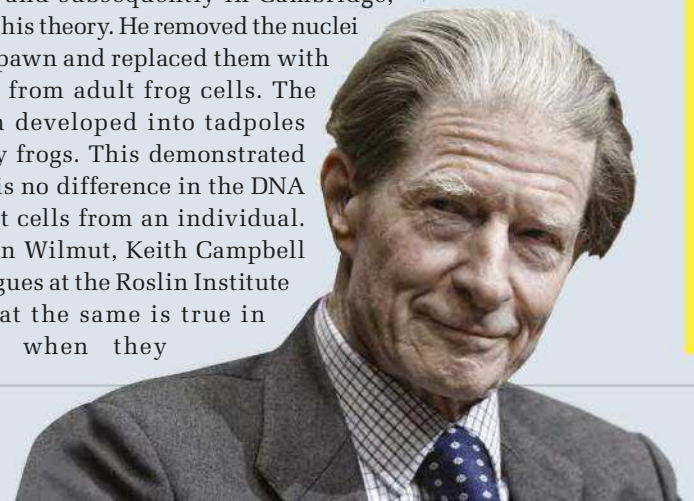
RIGHT: This model shows a nucleosome which is composed of DNA wound around so-called 'histone' proteins

BELOW: Sir John Gurdon won a Nobel Prize for his pioneering work on frog genetics



HOW IT WORKS

How epigenetic modifications are expressed within the structure of our DNA, and passed on to our children

The DNA in our cells is not a long, stringy molecule. Instead, it's curled around proteins called histones. DNA winds around a cluster of eight histone proteins, then continues on a little before winding around another cluster. This process is repeated millions of times in every cell. It allows our cells to package about two metres of DNA into a nucleus only a fraction of a millimetre in diameter.

When a cell receives signals from the environment, tiny chemical modifications are made to the DNA and to the histone proteins. These are called epigenetic modifications, and they regulate expression from the DNA. There is a huge range of different modifications, especially to histone proteins, and they come in a dizzying array of combinations, creating vast flexibility in gene expression. And because cells pass on the same pattern of epigenetic modifications to daughter cells when they divide, these effects on gene expression are maintained.

EVERYDAY EPIGENETICS: CATS

Almost all tortoiseshell cats are female. The orange and black coat colour genes are carried on the female sex chromosomes, known as X chromosomes. One of each pair of X chromosomes is randomly silenced by epigenetics early in development, and this creates the beautiful patchwork fur patterns.

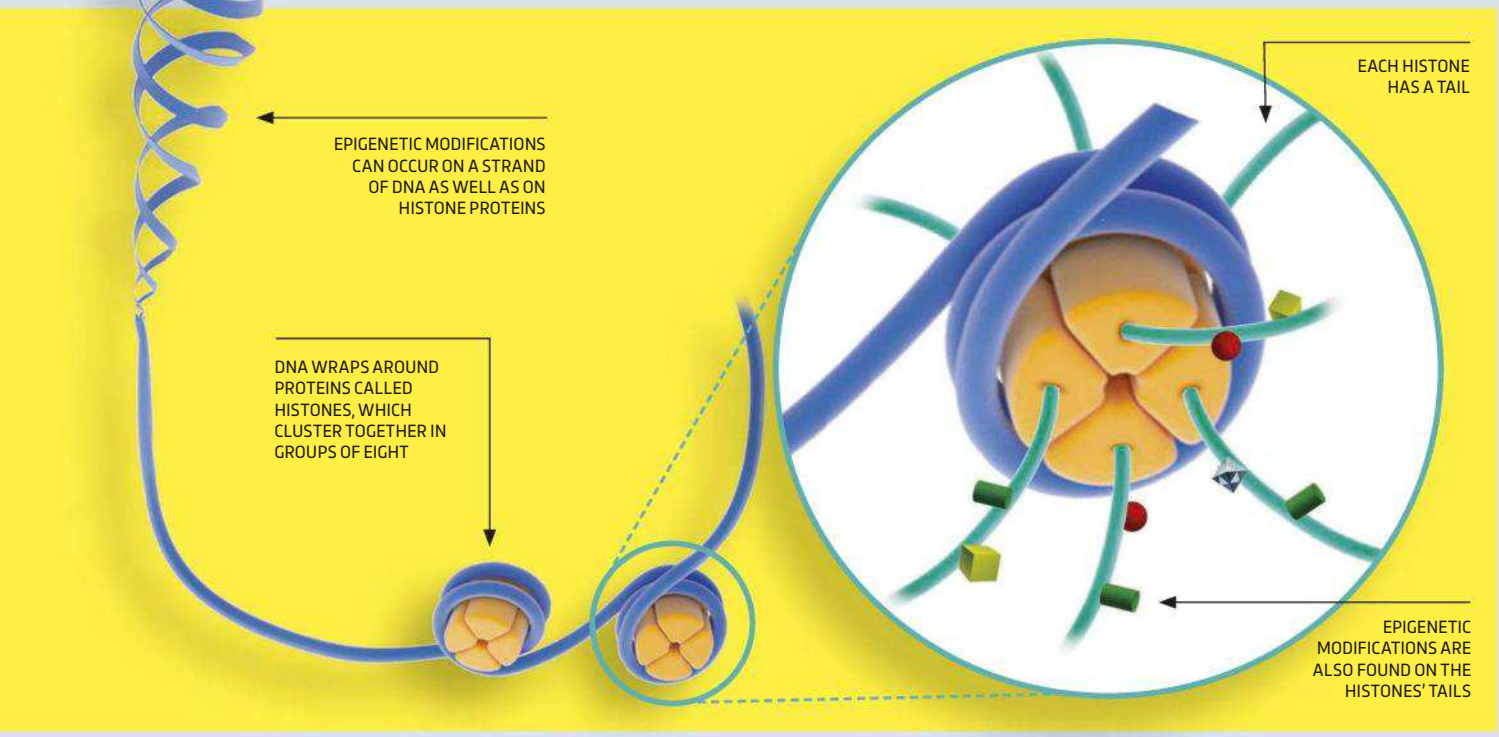
cloned Dolly the sheep, using a nucleus from an adult sheep mammary cell.

THE BIRTH OF EPIGENETICS

In 2012, Gurdon was awarded a Nobel Prize for his work. Over the decades since his discovery, researchers – such as those at the multinational Roadmap Epigenomics Project – have made enormous strides in identifying the mechanisms behind epigenetic phenomena. These mechanisms are dependent on tiny chemical modifications to DNA, and to certain proteins called histones that are associated with our genetic material (see 'How it works' below). These modifications are referred to as 'epigenetic modifications'.

Lots of different enzymes can add or remove epigenetic modifications at different positions on the genome, and hundreds of other proteins can bind to various combinations of modifications and change the way the genome is used. These epigenetic modifications change in response to environmental stimuli, and allow our cells to adapt their expression of particular genes to a change in circumstance. Epigenetics therefore provides the bridge between nature (our genome) and nurture (our environment).

Some epigenetic responses to the environment are established early in life, such as in the first trimester of human



Babies conceived during the 'Hunger Winter' showed increased levels of adult obesity

ABOVE LEFT: Dutch children during the 'Hunger Winter' of 1944–45. The epigenetic effects of the Netherlands' wartime famine are still being experienced today

ABOVE RIGHT: The original invitations to parents to take part in the Avon Longitudinal Study of Parents and Children, also known as 'Children of the 90s'

pregnancy. An example of this has previously been seen in the Netherlands. Towards the end of WWII, certain regions of the country suffered catastrophic food shortages. Calorie intake dropped to less than 40 per cent of normal levels for a period of several months that became known as the 'Hunger Winter'. Babies conceived during this period were normal at birth, but as they matured they began to show increased levels of adult obesity and Type 2 diabetes. This is because their genes were epigenetically modified during early development to enable the individuals to make the best use of what scarce nutrition there was. This would be an advantage if the famine had continued, but in a society with limitless access to food, this epigenetic alteration is problematic.

Epigenetics provides researchers with a new way of understanding the foetal origins of adult disease, and is actively investigated in long-term epidemiological studies such as the Avon Longitudinal Study of Parents and Children that has been following nearly 15,000 families since the early 1990s. Rodents that experience traumatic early life experiences establish epigenetic neuronal patterns that affect their stress levels in adulthood. Similar mechanisms may underlie the negative effects that early childhood abuse has on adult mental health in humans.

EPIGENETICS AND HEREDITY

We know that genetic information is passed on from parent to child, but what about epigenetic information? In the 1980s, Prof Azim Surani at the University of Cambridge demonstrated that this does happen. In fact, successful reproduction in placental mammals positively requires transmission of appropriate epigenetic modifications from both parents. Using in vitro fertilisation techniques in mice, Surani showed that live animals can only be born if an egg and a sperm nucleus

EVERYDAY EPIGENETICS: SEA BASS

Mammal gender is genetically determined, based on the presence or absence of a Y chromosome. However, in young European sea bass, water temperature causes epigenetic changes, and this determines their gender. There's a similar mechanism in crocodiles. Therefore global warming may disrupt sex distribution.

The cloning of Dolly the sheep in 1996 proved that stem and adult cells in mammals both contain the same DNA information

fuse together in an egg. No live young were born if he used two egg nuclei or two sperm nuclei, even though at a genetic level all three situations were identical.

More evidence that epigenetic information is passed on from parent to child comes from a strain of mice called the 'Agouti viable yellow'. These mice can be fat and golden, skinny and brown, or all types in-between. All Agouti viable yellow mice are genetically identical; their differences are caused by epigenetic modifications to a certain region of the genome. The offspring tend to look like their parents, showing that they are inheriting this epigenetic information. But some of the baby mice are different from their parents, which demonstrates that the transmission of epigenetic info is fuzzy. The proportion of the offspring that have a different appearance varies in response to environmental stimuli, such as giving alcohol to the mothers.

So according to the research, epigenetic information is passed on from parent to offspring and can also be influenced by the environment. This raises the next question: can epigenetically-mediated responses to the environment be passed on from parent to offspring?

Classical Darwinian models of evolution would say no, as this idea has more in common with the theory of inheritance of acquired characteristics proposed by Jean-Baptiste Lamarck, the 19th Century French naturalist who was Darwin's main rival. But this certainty is increasingly coming under threat. There are some indications from the Dutch Hunger Winter subjects, for example, that the metabolic defects suffered by those who experienced famine in childhood are now being passed on to future generations.

Unfortunately, it is incredibly difficult to separate the effects of genetics, epigenetics and environment in human populations. So for greater certainty, researchers have once again turned to rodents. A number of studies have shown

EVERYDAY EPIGENETICS: TWINS

Identical twins are rarely exactly the same, despite sharing the same DNA code. One twin may have a devastating disease while the other is healthy. This reflects epigenetic differences, usually as a combination of responses to the environment and also random variability in the epigenetic modifications in their cells.

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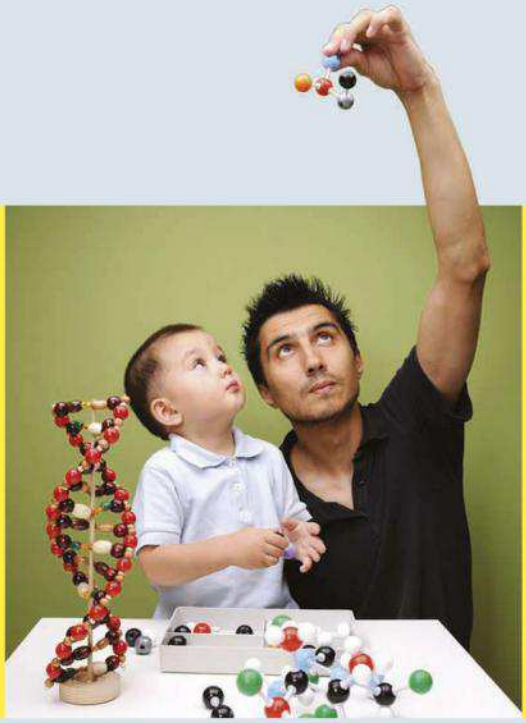

NATURAL SELECTION

The process that causes evolution

Natural selection is a process driven by random variation – changes in a DNA sequence that are passed on from parent to child. If a particular variation confers an advantage under the prevailing environmental conditions, the individual carrying that variation has more chance of surviving to breeding age, and of breeding successfully.

This will pass on their DNA sequence, and increase the number of individuals in the next generation carrying that variation. When this continues over millennia, it drives the process of speciation. And even within shorter periods, it can affect how populations develop. For example, the variation in the haemoglobin gene that makes people susceptible to the genetic condition beta thalassemia also gives them a degree of protection from malaria. This is why levels of beta thalassemia are highest in countries where malaria has historically been endemic, such as Greece and Turkey. Epigenetic modifications may also be passed on from parent to child.

that when male rodents are malnourished, their offspring are metabolically impaired. But it's experiments using fear-conditioning techniques that have really shaken up the field. Male mice were trained to associate a particular smell with an electric shock, and after repeated exposures the smell alone was enough to trigger a fear response. When the offspring of the mice were tested, they were also frightened by the smell, even though they had never been exposed to the electric shock. The mice also had the same epigenetic modifications to key genes in the brain as their traumatised fathers.

Does this mean that the Darwinian model of evolution is dead? Of course not. Most of the time, eggs and sperm are protected from epigenetic changes to the environment, and relatively few newly established modifications are likely to make it through to the next generation. Even when they do, the modifications and the effects they cause tend to die out within a few generations. This is what we would expect, as epigenetic alterations are intrinsically unstable.

But this transfer of epigenetic information across generations probably provides short-term advantageous adaptations to temporary changes in the environment without affecting the underlying genetic code that has evolved over thousands of years. The epigenetic inheritance takes place under certain conditions, but is unlikely to be a major player in long-term natural selection.

There is a tendency to 'blame' epigenetic inheritance for current problems, such as the human obesity epidemic

Despite this, there is an increasing and facile tendency to 'blame' epigenetic inheritance for current problems, such as the human obesity epidemic. Fascinating though this field is, it's not a get-out. The most important things that are happening to your health are happening here and now: no one gains weight in 2015 just because their grandad had a fondness for doughnuts in the 1960s!

EVERYDAY EPIGENETICS: BEES

Queen bees are physically very different from workers, and can live 20 times longer. But there's nothing genetically special about queen bees: they are just the product of a different feeding regime in early life. This leads to epigenetic modifications that maintain queenly gene expression patterns.

Nessa Carey is a molecular biologist and author of the books *Junk DNA* and *The Epigenetics Revolution*.

BBC RADIO 4

Listen to *All in the Womb* which discusses epigenetics *bbc.in/1SabzAE*

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THE VIRUSES THAT MADE US HUMAN

Viruses give us infections, from the common cold to Ebola and HIV. But new research shows that they may also have played a key role in shaping the evolution of *Homo sapiens*

WORDS: **KAT ARNEY**

Zika, Ebola, flu – we're familiar with the viruses that plague humanity. But while we know they make us sick, it may be surprising to discover that, over millions of years, we've managed to harness and domesticate these crafty invaders. From the earliest stages of life to the smiles on our faces, viruses have had a huge influence on our human species.

Viruses are little more than a string of genes (usually in the form of a molecule called RNA) packaged in a protein coat, and they all work in the same basic way. Once a virus has infected a cell, it hijacks the cell's own molecular machinery to copy its genes and churn out viral proteins. New viruses are assembled from these freshly manufactured parts, which eventually burst out in search of new cells to attack (see page 26).

For most viruses, such as flu, the story ends there. But a handful of retroviruses – including HIV – are even sneakier, smuggling their way into our DNA. They insert themselves randomly into the genome of an organism, lying low until the time is right to start virus production again. But once a retrovirus has got into an organism's DNA, there's no guarantee that it will stay put. The genetic instructions can be 'read' from the embedded virus, converted into DNA and then pasted into another location in the genome. Repeat this cycle again and again, and multiple copies of the viral DNA quickly build up.

Over millions of years, these viral DNA sequences randomly mutate and change, losing their ability to break free from their host cells. Trapped inside the genome, some of these

ILLUSTRATION: CHARIS TSEVIS

Kat Arney co-hosts the BBC Radio 5 Live show *The Naked Scientists*

As well as being our genetic enemies, some of the viruses embedded in our genome have become our slaves

'endogenous' retroviruses can still jump around while others are stuck forever where they last landed. If any of these events happen in the germ cells that make eggs and sperm, they will be passed down the generations and eventually become a permanent part of an organism's genome.

Around half of the human genome is made up of millions of DNA sequences that can be traced back to long-dead viruses or similar 'jumping genes', known collectively as transposable elements or transposons. Some researchers would even put this figure up at 80 per cent, as ancient sequences are now degraded beyond the point of being recognisably virus-like, weathered within the genome like molecular fossils.

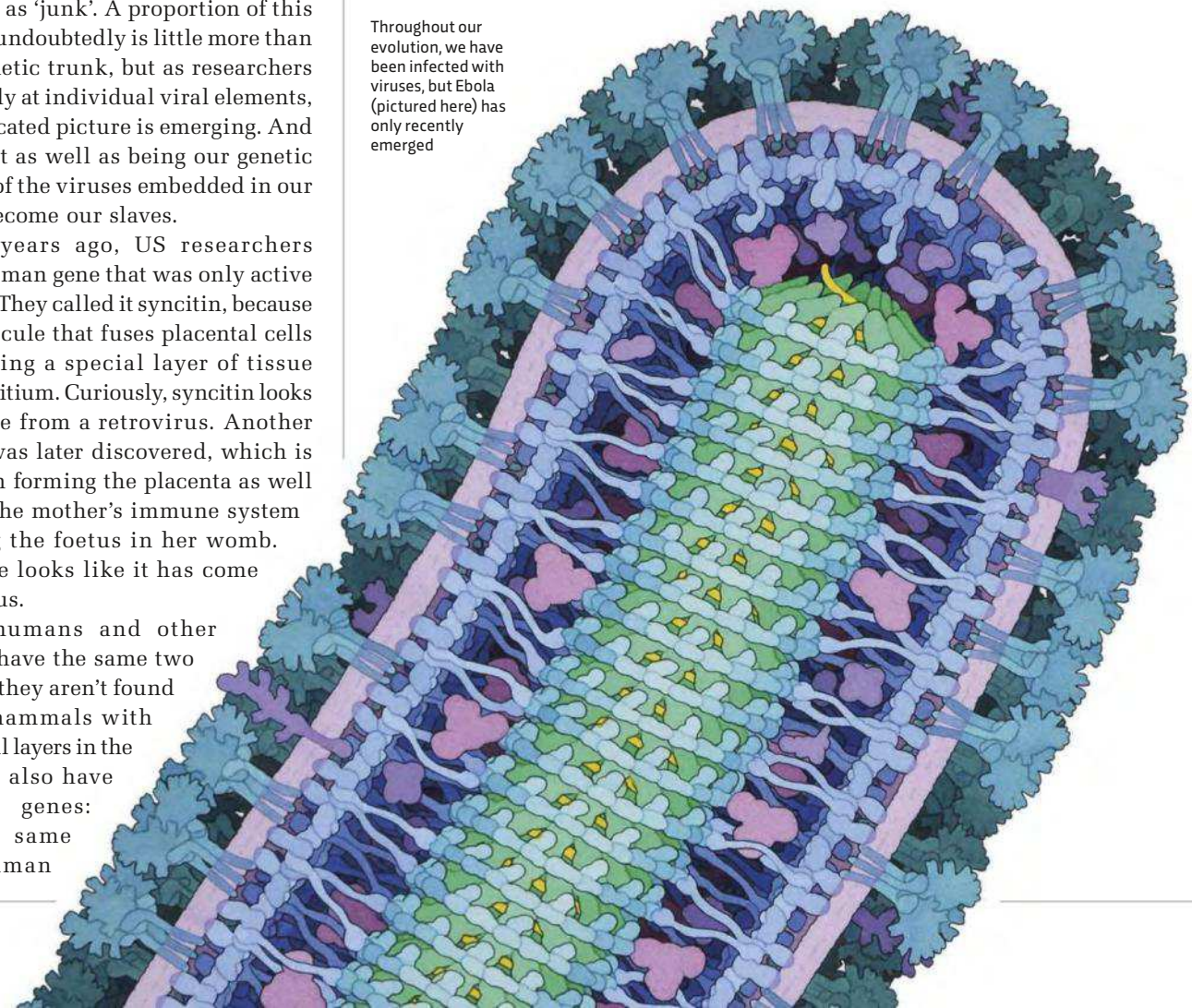
For many years, the large chunks of repetitive virus-derived DNA littering the human genome were dismissed as 'junk'. A proportion of this repetitive stuff undoubtedly is little more than junk in our genetic trunk, but as researchers look more closely at individual viral elements, a more sophisticated picture is emerging. And it turns out that as well as being our genetic enemies, some of the viruses embedded in our genome have become our slaves.

Around 15 years ago, US researchers discovered a human gene that was only active in the placenta. They called it syncitin, because it makes a molecule that fuses placental cells together, creating a special layer of tissue known as a syncitium. Curiously, syncitin looks a lot like a gene from a retrovirus. Another syncitin gene was later discovered, which is also involved in forming the placenta as well as preventing the mother's immune system from attacking the foetus in her womb. Again, the gene looks like it has come from a retrovirus.

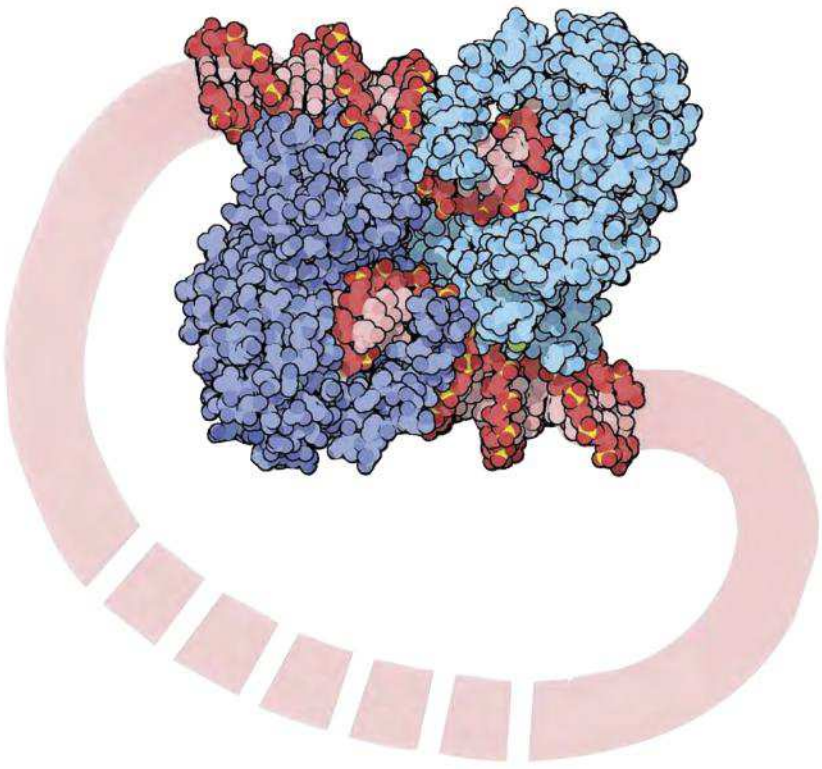
But while humans and other large primates have the same two syncitin genes, they aren't found in any other mammals with similar fused cell layers in the placenta. Mice also have two syncitin genes: they do the same job as the human version, but they look like completely different viruses. And there's another separate virally-derived syncitin gene in cats and dogs – both are descended from the same carnivorous ancestors.

Clearly, all these mammalian species were infected by certain viruses millions of years ago. Over time, those viruses have been harnessed to play a key role in placental growth, making them a permanent fixture in our genome. Intriguingly, pigs and horses don't have a layer of fused cells in their placenta, and they also don't have any genes that look like virally-derived syncitins. So maybe they never caught one of these fusing viruses.

While the case of syncitin reveals the wholesale adoption of a virus gene to do our bidding, there are many more examples of how



Throughout our evolution, we have been infected with viruses, but Ebola (pictured here) has only recently emerged



ABOVE LEFT: Barbara McClintock first identified the effects of 'jumping genes' in maize

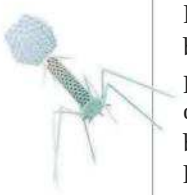
ABOVE: Two molecules of the 'cut and paste' enzyme transposase (blue and purple) grip onto the free ends of a DNA transposon (pink), ready to insert it into a new site within the genome

ancient viral sequences can influence gene activity in today's humans. Back in the 1950s, detailed work by the long-overlooked American geneticist Barbara McClintock revealed that 'jumping genes' could affect the genome of maize plants. And just like the 'jumping genes' McClintock identified in maize, the endogenous retroviruses that lurk in our own human genome have been on the move over millions of years, jumping around at random and altering the activity of genes in their immediate vicinity.

Our cells invest a lot of energy in attempting to stop these viral elements from going on the hop. They're labelled and locked down with chemical tags, known as epigenetic marks. But, as the viral elements move, these molecular silencers move with them, so the viral sequences' effects can spread to neighbouring genes wherever they land.

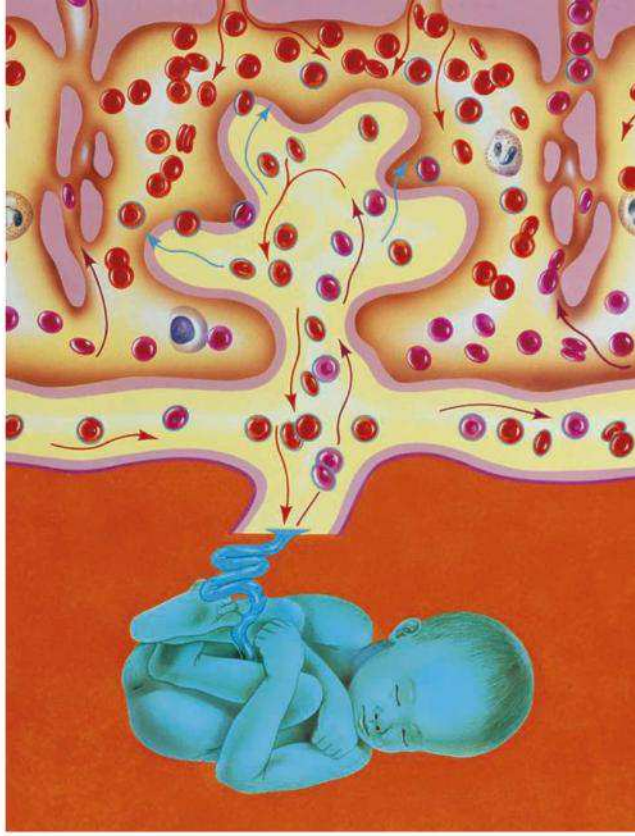
Conversely, viruses are also full of DNA sequences that attract molecules which switch genes on. In a functional retrovirus, these 'switches' activate the viral genes so it can become infectious again. But when a virus-like sequence gets spliced into another region in the genome, this ability to act as a genetic switch can end up going rogue.

In 2016, scientists at the University of Utah found that an endogenous retrovirus in the human genome – which originally came from a virus that infected our ancestors roughly 45 million to 60 million years ago – switches on a gene called AIM2 when it detects a molecule called interferon, which is the 'danger signal' that warns the body that it's suffering a viral infection. AIM2 then forces the infected cells to self-destruct, to prevent the infection from spreading any further. These ancient viruses have become 'double agents', helping our cells to tackle other viruses that are trying to attack us.



Another example of a virus that may have shaped our species is found near a gene called PRODH. PRODH exists in our brain cells, particularly in the hippocampus. In humans, the gene is activated by a control switch made from a long-dead retrovirus. Chimpanzees also have a version of the PRODH gene, but it's not nearly so active in their brains. One possible explanation is that an ancient virus hopped a copy of itself next to PRODH in one of our long-dead ancestors, millions of years ago, but that this didn't happen in the ancestral primates that went on to evolve into today's chimps. Today, faults in PRODH are thought to be involved in certain brain disorders, so it's highly likely to have had at least some kind of influence on the wiring of human brains.

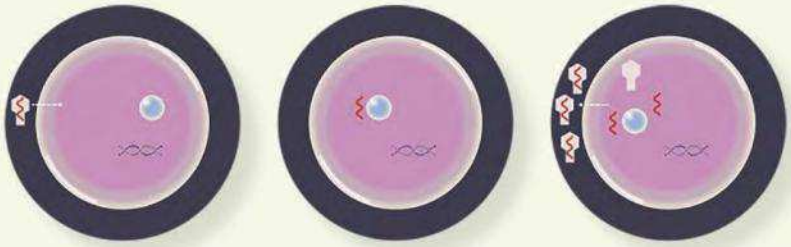
Similarly, variations in genetic switches are responsible for the differences between the cells that build our human faces as we grow in the womb and those of chimps. Although our genes are virtually identical to chimpanzee genes, we certainly don't look the same. So the difference must lie in the control switches. Judging by their DNA sequences, many of the switches that are active in the cells that grow our faces seem to have originally come from viruses, which must have hopped into place



HOW VIRUSES WORK

VIRAL PROTEIN | VIRAL GENES | REVERSE TRANSCRIPTASE | CELL MACHINERY | HOST CELL DNA

MOST VIRUSES (E.G. FLU)

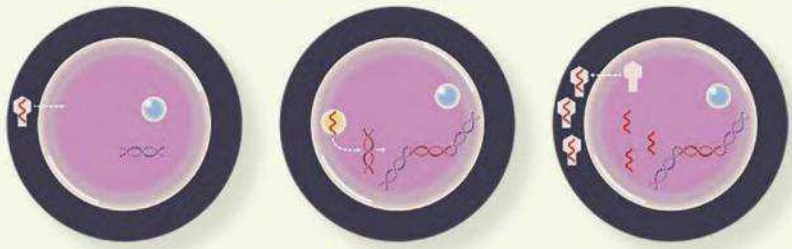


INFECTION
First of all, the virus infects a host cell. Its protective protein coat breaks down and the virus releases its genes.

HIJACK!
The virus then takes over the cell machinery that makes genes and proteins. The virus forces it to copy its own genes and make viral proteins.

DUPLICATION
New viruses will be assembled inside the host cell. Eventually, they will break out and go in search of new hosts to infect.

RETROVIRUSES (E.G. HIV)

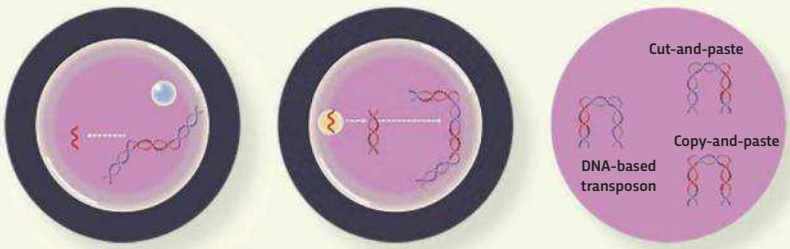


INFECTION
The virus infects a host cell. Its protein coat is broken down and the viral genes (in the form of a DNA-like molecule called RNA) are released into the cell.

INSERTION
In the cell, the viral RNA uses an enzyme called reverse transcriptase to convert its RNA into DNA, which it inserts into the host's genetic material.

DUPLICATION
Once integrated into the cell's DNA, the virus uses the cell machinery to create more viral proteins and RNA, which assemble on the cell's surface.

TRANSPOSONS (JUMPING GENES)



CREATION
Retroviruses embedded in the cell's DNA create viral RNA.

INSERTION
Reverse transcriptase is then used to convert the viral RNA into viral DNA. The viral DNA is inserted somewhere else into the host's DNA.

OTHER METHODS
Not all transposons use the RNA copying step. Others can move through the genetic sequence using DNA-based 'cut-and-paste' or 'copy-and-paste' methods.

sometime in our evolutionary journey towards becoming the flat-faced species we are today.

THE VIRUS TAMERS

As well as searching for examples of long-dead viruses that have altered our biology, scientists are searching for the control mechanisms that underpin their effects. The key culprits are special silencing molecules called KRAB Zinc Finger Proteins (KRAB ZFPs), which grab hold of viral sequences in the genome and pin them in place. Prof Didier Trono and his team at the University of Lausanne in Switzerland have discovered more than 300 different KRAB ZFPs in the human genome, each of which seems to prefer a different virally-derived DNA target. Once there, they help to recruit the molecular machinery that turns genes on or off.

"These KRAB ZFPs have been viewed as 'killers' of these endogenous retroviruses," Trono explains. "But they are actually exploiters of these elements that allow the organism to exploit the wealth of possibility that resides in these viral sequences."

Trono and his team believe that KRAB ZFPs are the missing link between viral sequences that are actively harmful and those that have become tamed control switches. They have evidence that the proteins have evolved alongside the viral elements in a kind of 'arms race', initially suppressing them but eventually

overpowering them. "We think that what they do is domesticate these elements," Trono says. "By domestication, I mean not just making sure that the viruses stay put, but turning them into something beneficial for the host, which is a very refined way of regulating gene activity in all possible cells and situations."

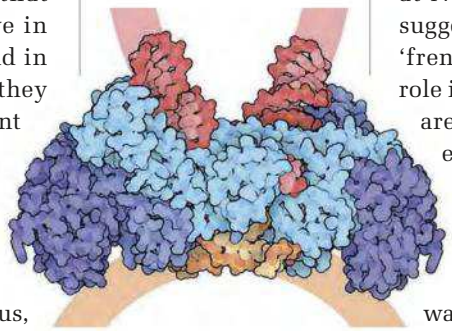
Supporting this idea is the finding that distinct groups of KRAB ZFPs are active in different types of cells. They're also found in specific patterns in different species. If they were just suppressing viruses, the argument goes, the same array of proteins should be present in all cells. What's more, why would they be found bound to the many thousands of long-dead viral elements that Trono and his team have identified? There's no point suppressing a dead retrovirus, so they must be playing an important role in controlling gene activity.

Although his idea is still a little controversial, Trono sees the KRAB ZFPs as a force of viral slavedrivers, harnessing these elements to do our bidding and turning them into genetic control switches. Over many millions of years, this could have been a powerful motor for creating new species. For example, if a virus randomly goes on the hop in one ancestral creature and not another and is then tamed over time by a KRAB ZFP, it will create new control switches that could have a big impact on an animal's appearance or behaviour. What's more, these jumping elements become more active during times of environmental change. As times get tough, species need to find new ways to adapt or they will die out. Activating these mobile elements reshuffles the genome, throwing up novel genetic variations that provide rich fodder for natural selection to work on.

ABOVE LEFT: **Viruses may have played a key role in the evolution of the human placenta**

ABOVE RIGHT: **HIV virus in human lymph tissue**

BELOW: **The enzyme HIV integrase allows HIV to embed itself in a host cell's DNA**

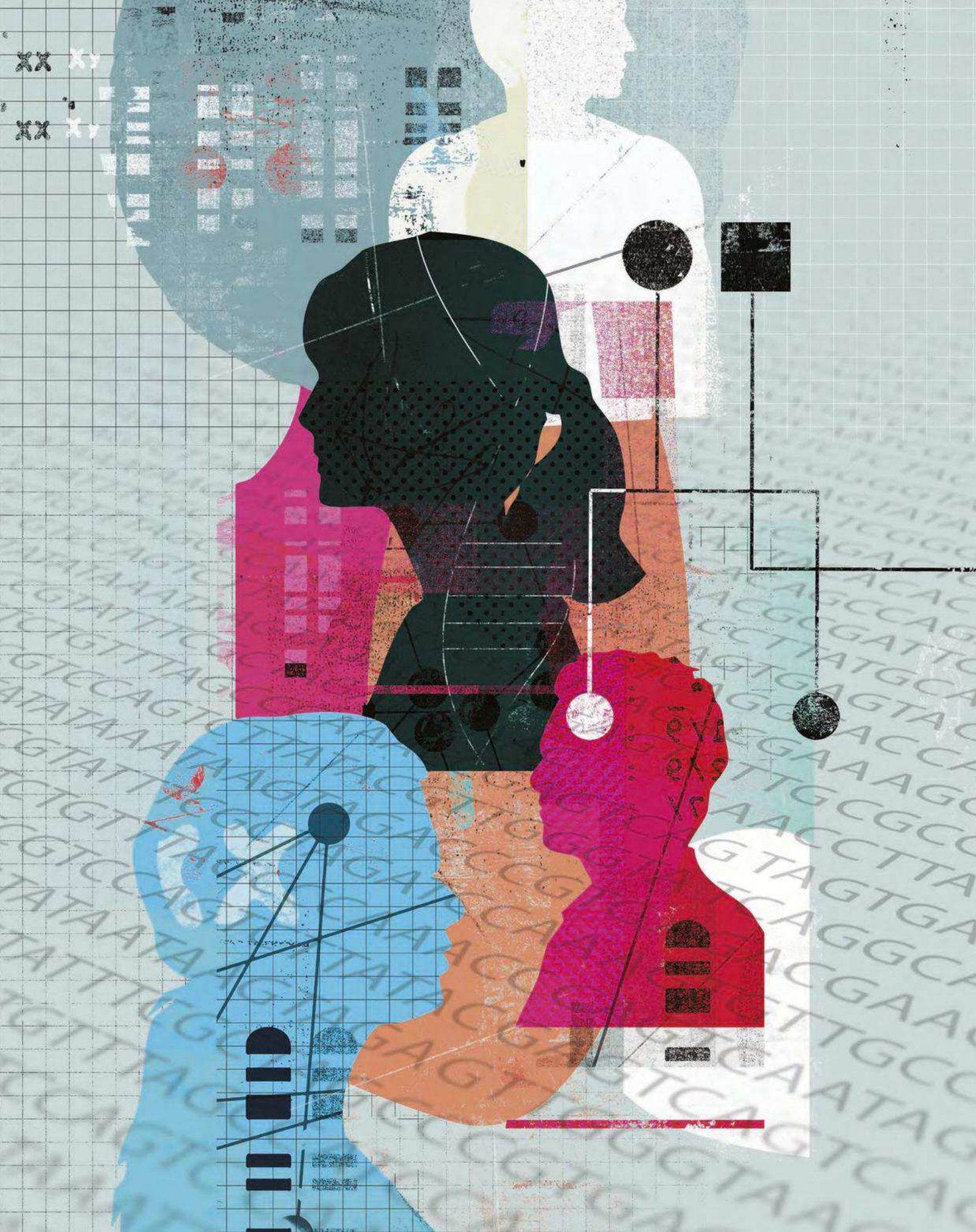


Kat Arney is a science writer and broadcaster who presents *The Naked Scientists* every week on BBC Radio 5 Live. Her latest book is *How To Code A Human.*

So it's clear that the viruses trapped in our genome have brought us enormous benefits on an evolutionary timescale. But they aren't all so helpful. Around one in 20 human babies is born with a new viral 'jump' somewhere in its genome, which could deactivate an important gene and cause disease. There's increasing evidence that jumping transposons contribute to the genetic chaos inside cancer cells. And intriguing research suggests that brain cells are good locations for reactivating jumping genes, possibly increasing the diversity of nerve cells and enhancing our brainpower but also potentially causing ageing-related memory problems and conditions such as schizophrenia.

So are these viruses inside our DNA our friends or our enemies? Paolo Mita, a postdoctoral fellow researching transposons at NYU School of Medicine in New York, suggests that it's a bit of both. "I call them our 'frenemies', because when you look at their role in one human lifespan, most likely if they are mobilised there are going to be negative effects," he explains. "In the short term, they are our enemies. But if you are looking across time, these elements are a powerful force of evolution and they are still active in our species today. Evolution is just the way that organisms respond to changes in the environment, and in this case they are definitely our friends because they have shaped how our genome works now."

And are the viruses infecting us today, such as HIV, going to have an impact on our evolution in the future? "Of course! The answer is why not?" laughs Mita. "But it will be many generations until we can look back and say this evolution has happened. But you can see the remnants of previous arms races in the genome between the endogenous retroviruses and the host cells. It's a continuous battle, and I don't think it has ever stopped."



THE A TO Z OF YOU

Our bodies contain some 30 trillion cells, and an ambitious project aims to map the molecular signature of every single one

WORDS: **KAT ARNEY**

Mapping the human body is one of biology's oldest endeavours. By studying the battered bodies of Roman gladiators, the 2nd-century philosopher-surgeon Galen of Pergamon wrote medical texts that stood as the pinnacle of anatomical knowledge for more than 1,000 years, until the Flemish doctor Andreas Vesalius came up with more accurate works. But it wasn't until the invention of the first practical microscope in the mid-1600s, a century after Vesalius's death, that curious scientists could finally begin to study cells – the building blocks that make up our tissues and organs.

Just as studying subatomic particles has helped physicists unravel the workings of the cosmos, so biologists have found that zooming in on our individual cells can reveal new insights into the human body. For a long time, this was the domain of pathologists, studying the physical appearance of cells and tissues, along with a relatively limited number of molecular markers. But, backed by the exciting new science of single-cell genomics (see 'How it works', p30) a project called the Human Cell Atlas is aiming to create the ultimate inventory of the human body, mapping every single one of our cells in intricate detail. And the resulting guidebook could revolutionise our understanding of health and disease.

CELLULAR SCIENCE

It's long been clear that cells in different organs behave in their own distinctive ways. For example, spherical immune cells are primed to recognise infections, while spidery nerve cells crackle with hundreds of connections. Nevertheless, each cell still has the same basic set of instructions in the form of the human genome, encoded within our DNA. The thing that makes each cell type different is the particular set of genes active within it, producing molecular messages called RNA. And because a particular pattern of gene activity will be unique to a specific cell type, the RNA made within it will be unique too, acting as a kind of molecular fingerprint.

For decades researchers have been able to measure the activity of genes in different cell types (known as gene expression) by mashing up millions of cells and analysing the different RNAs to see which genes are switched on and off.

Yet this is only an average and doesn't pick up differences between individual cells. It's like looking at a crowd from a distance and only seeing a colourful blur, rather than the

GETTY X2

exact hue of each person's shirt. But thanks to recent advances in technology, we can now zoom in to look at gene activity in a single cell.

A typical human body contains around 30 trillion cells, but while it's often said that there are around 200 types, detailed molecular analysis has revealed that this is a huge underestimate. Is every cell in the liver exactly the same, or have we only been measuring averages? What about the billions of neurons in the brain, or the multitude of distinct immune cells? These questions provided the spark for the Human Cell Atlas, which aims to map gene expression patterns in billions of individual cells.

"WE COULD TAKE TINY SAMPLES FROM MANY DIFFERENT PEOPLE AND STITCH THEM TOGETHER INTO A KIND OF UNIVERSAL ATLAS"

THE JOURNEY BEGINS

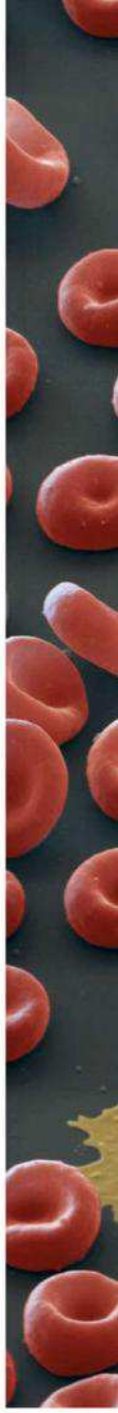
The idea flickered into life in 2012 when geneticist Dr Sarah Teichmann came to the Wellcome Trust Sanger Institute near Cambridge to set up a research group studying gene activity in single cells in the mouse immune system. Talking to her new colleagues, she realised that her techniques might solve a bigger challenge.

"Despite centuries of microscopy, we don't fully understand the different cell types," she says. "When I came to the Sanger Institute we started bouncing ideas around. It was a bit utopian because the technology wasn't there yet, but we thought what if some day it would be possible to atomise a human body – take a human and look at all their cells. Of course, you're not vaporising a whole person, but we thought we could take tiny samples from many different people and stitch them together into a kind of universal atlas."

With trillions of cells to analyse, this isn't the kind of task that a single lab, or even a single institute, can handle alone. Teichmann and her colleagues soon realised that other researchers were having similar thoughts – notably Dr Aviv Regev at the Broad Institute in Massachusetts – and began to build an international consortium of single-cell enthusiasts ranging from geneticists and molecular biologists to surgeons and machine-learning specialists. The team has begun studying five types of tissue: the brain, the immune system, epithelial tissue (which lines the surfaces of organs and blood vessels), and foetal and placental cells. As well as cataloguing the cells of healthy people, part of the project will be to understand how cells change their activity when we get sick, so cancer cells are on the initial list, too (see 'Target cells', p32).

ROBOT RESEARCHERS

The scale of the Human Cell Atlas and the accuracy required means that this is no longer the kind of work that can be done by hand. To find out more about the technology involved, I visited Dr Stephan Lorenz. He heads up the single-cell genomics facility at the Sanger Institute, where much of the work for the Human Cell Atlas will be carried out.

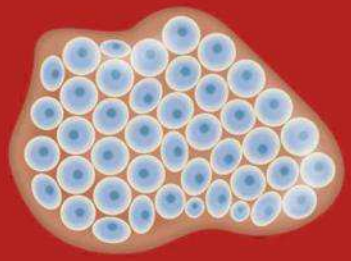


SCIENCE PHOTO LIBRARY, WELLCOME IMAGES ILLUSTRATIONS: ACUTE GRAPHICS

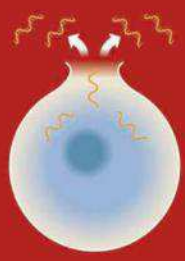
RIGHT: Modern images of blood cells taken with scanning electron microscopes (main image) offer far more detail than earlier microscope images, such as those published in 1845 (inset)

HOW IT WORKS: SINGLE-CELL GENOMICS

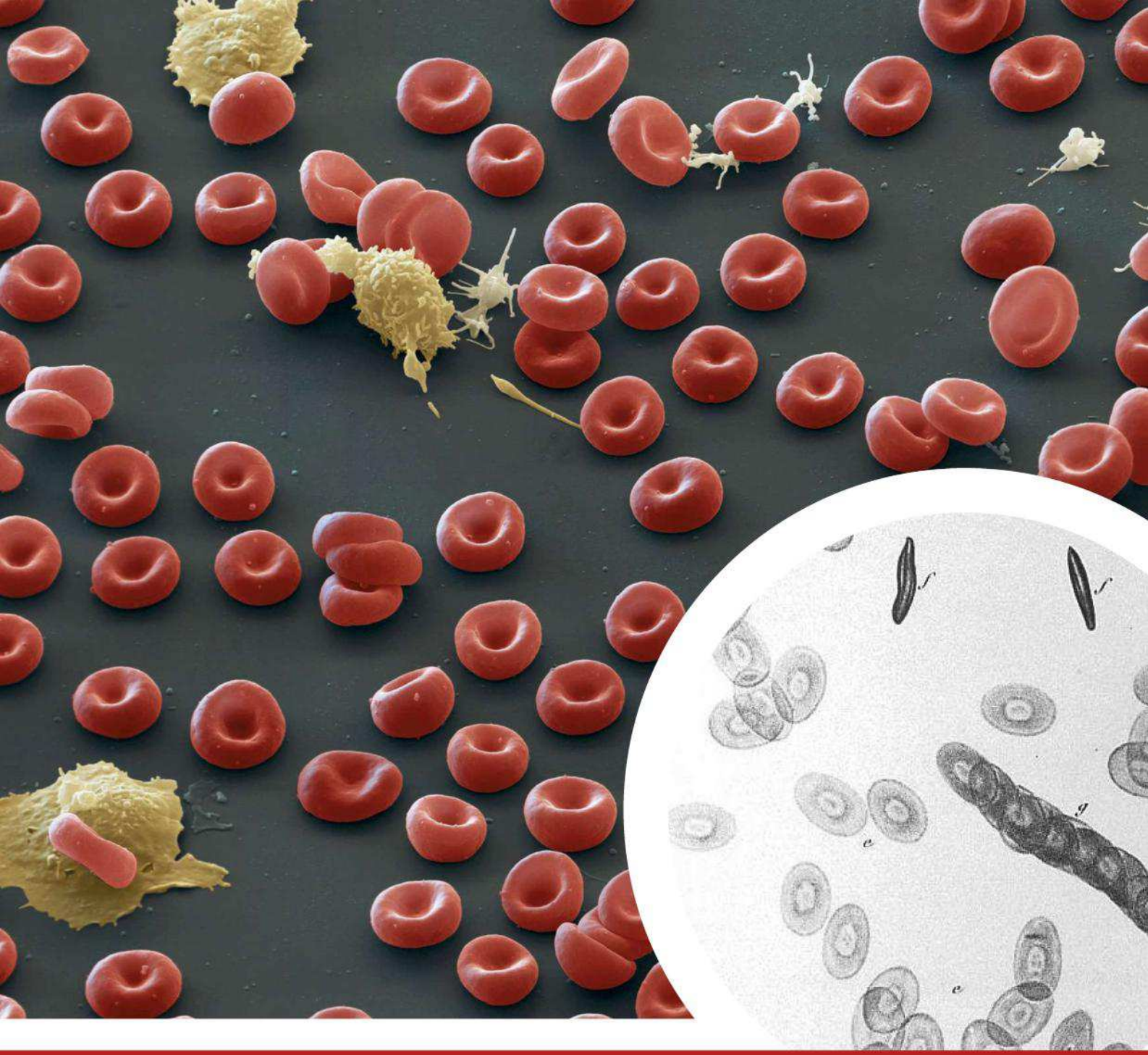
In order to measure the gene activity in a single cell, you need to isolate its RNA – the molecular messages produced when genes are switched on. By comparing the sequences of these messages with the whole genome (the complete set of DNA contained inside every cell), researchers can figure out which genes are being expressed in any particular cell at that time.

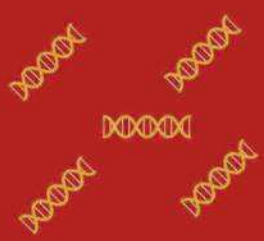


1 Separate tissue sample into single cells, using high-powered focused laser beams, enzymes or other techniques.

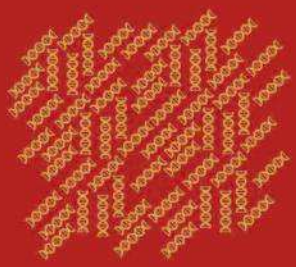


2 Break open each cell to release the RNA messages.

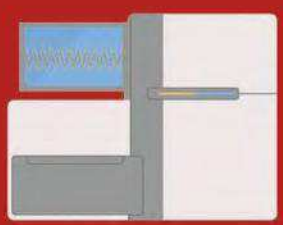




3 Convert the RNA into DNA – this process is known as reverse transcription.



4 Amplify the DNA thousands or even millions of times to get enough material to sequence.



5 Read the DNA using next-generation sequencing tech.

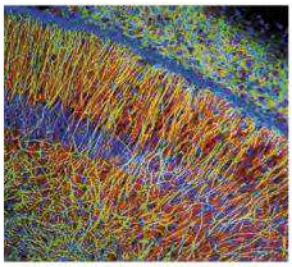
6 Analyse results to work out which genes are active, producing a gene expression profile for that cell. Repeat for cells around the body.

TARGET CELLS

THE HUMAN CELL ATLAS IS INITIALLY FOCUSED ON FIVE TYPES OF CELL...

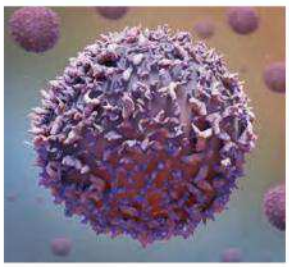
Brain

The brain is probably the most complex organ in the body, made up of more than 86 billion nerve cells (neurons). By mapping all the patterns of gene activity in different brain cells, researchers hope to understand how neurons wire up and communicate, and what goes wrong in psychiatric and neurodegenerative illnesses.



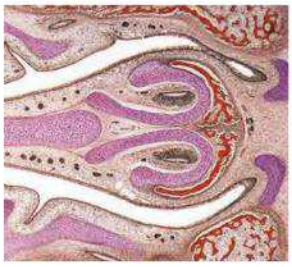
Immune system

There are hundreds of types of cell in the immune system alone, each with distinct roles in spotting and responding to infections or disease. Analysing each cell type will reveal the changes that happen as the immune system fires into action, and will shed light on autoimmune conditions and allergies.



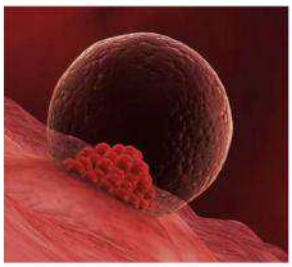
Epithelial cells

Epithelial cells are one of the most versatile cell types. They make the linings of our organs, ranging from the tubes of the gut to the delicate air sacs of the lungs. Establishing how epithelial cells carry out such a diverse range of roles will explain how organs grow and are affected by diseases such as cancer.



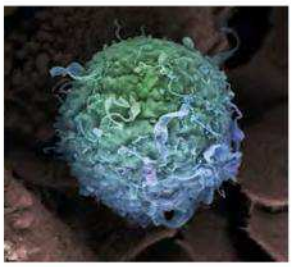
Placenta and foetus

Studying these tissues will reveal how we grow and develop in the womb, and how a healthy placenta develops to provide oxygen and nutrients. This will give us vital clues for understanding what has gone wrong in babies who are born with developmental disorders, or when a pregnancy is lost.



Cancer

By analysing gene activity in single cancer cells, researchers hope to identify the changes that trigger the growth and spread of tumours. They are also searching for clues to explain how these rogue cells can develop resistance to therapy, with the aim of finding ways to prevent the disease coming back again after treatment.



"WE CAN NOW UNDERSTAND HOW CELLS 'THINK AND FEEL' AND SEE INSIDE THE 'MIND' OF A CELL"

"Over the last couple of years there's been an explosion of methods that allow us to measure these tiny quantities of RNA that are present in a single cell," he says. "We can now understand how cells 'think and feel' and see inside the 'mind' of a single cell. By looking at the messages in cells we can infer their function and even their identity." What's more, he explains, he can even see how individual cells in the immune system change when they are activated to fight infection, or watch the genes that are switched on and off as one cell splits into two.

Yet RNA messages aren't the only thing that gives a cell its identity. RNA carries instructions to make proteins, which build physical structures inside cells and carry out biological functions in the body (for example, digestive enzymes in the stomach or keratin proteins that make up our skin and hair). Lorenz and his colleagues are now developing methods to analyse all the proteins inside a single cell.

It currently takes about three weeks to analyse the RNA in an individual cell, though the process is speeding up all the time. Perhaps an even bigger challenge than analysing all of the cells is coping with the quantity of data generated. Around 850,000 messages are sequenced per cell. Multiply that by millions of cells, and it quickly adds up.

To help with this, the Human Cell Atlas consortium secured funding from the Chan Zuckerberg Initiative (set up by Facebook founder Mark Zuckerberg and his wife Priscilla Chan) to develop ways to process and present the torrent of information coming from the sequencing labs.

Making the Atlas searchable and usable is vital if it's to become a meaningful resource for scientists. Although Teichmann doesn't yet know how the data will be presented, she

A laboratory at the Sanger Institute, where a lot of the Human Cell Atlas research will be carried out

GETTY X5, SANGER INSTITUTE

does have one fun idea. "The really futuristic vision is that we'll all be wearing virtual reality headsets and be able to look at a virtual body to point out parts that we want to see," she says.

MAPPING THE FUTURE

It's still early days for this ambitious project, which kicked off in October 2016, but Teichmann thinks it's feasible. "I'd say for a draft Atlas we need to analyse between 30 million and 1 billion cells," she explains. "Over the last eight years, there's been an exponential decrease in cost per cell and an exponential increase in the number of cells per experiment. If that trend continues then we're in good shape."

As well as satisfying our scientific curiosity about what we're all made of, Teichmann sees the Atlas as a source of huge potential benefits for biomedical research, revealing leads for new drugs or finding molecules that act as biomarkers for diagnosing and monitoring disease. At a deeper level, she hopes it'll answer fundamental questions about the links between genes and health. As an example, she mentions the harmful mutation in a gene called CFTR that causes cystic fibrosis, which affects the lungs and other organs.

"We know that CFTR is active in the lungs, but it's expressed in other parts of the body, too. So you could interrogate the Human Cell Atlas and find those cells to understand why things are going wrong when it's mutated," she explains. "Or say you want to know the side effects of a drug that targets the product of a particular gene. You could search the Atlas to see where that gene is expressed – which organs, tissues and cells – and then predict what the anticipated side effects might be."

Understanding exactly what has gone wrong in a wide range of diseases, quickly identifying which cells and molecules are misbehaving, will help doctors to diagnose conditions faster and select the most appropriate treatment with less of the guesswork that goes on at the moment.

Ultimately, Teichmann and her team see the Human Cell Atlas as a fundamental resource that will one day have an impact on almost every aspect of biology and medicine. Perhaps we could even call it Human Genome 2.0.

"I like that!" she laughs. "The Human Genome Project was all about deciphering the DNA sequence, but the Human Cell Atlas is asking what does that sequence actually stand for? How is the genetic code read out to make a human body? It really is mind-blowing!"

Kat Arney is a science writer and broadcaster who presents *The Naked Scientists* every week on BBC Radio 5 Live. Her latest book is *How to Code a Human*.

Around **1 in 180 babies** are born with a chromosomal abnormality

72% OF WOMEN WHO INHERIT A HARMFUL MUTATION OF THE BRCA1 GENE AND 69% WITH A HARMFUL BRCA2 GENE WILL DEVELOP BREAST CANCER BY THE AGE OF 80

1.5 million

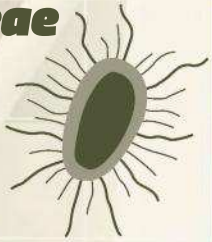
PEOPLE WORLDWIDE ARE AFFECTED BY RETINITIS PIGMENTOSA, WHICH CAUSES BLINDNESS, BUT IT CAN NOW BE TREATED BY GENE THERAPY

It is estimated that up to

75%

of cancer drugs do not work on the person they are prescribed for

A strain of the bacteria ***Enterobacteriaceae*** could be the next 'superbug', as this family of bacteria kill up to 50% of patients who get infected by them



XX DOWN'S SYNDROME IS CAUSED BY HAVING AN EXTRA COPY OF **CHROMOSOME 21**

If a mother and father both carry the faulty gene for a genetic condition, such as cystic fibrosis, there's a 25% chance of each child they have inheriting the genetic condition, and a 50% of their child being a carrier

WE KNOW OF OVER

100

GENES THAT ARE LINKED TO OBESITY

GETTY

YOUR HEALTH

A good diet and regular exercise will help keep you healthy. But they won't protect you from everything. Before you were even born, the launch codes for a host of diseases and conditions were programmed into your genes and no amount of healthy living can prevent any one of them from being triggered... But scientists are working to crack these codes and the results could lead to treatments and even cures, some of which may be tailored specifically to you.

ARE YOU A GENETIC SUPERHERO?

Recent research has revealed a handful of 'superheroes' walking among us, whose DNA gifts them with resistance against serious diseases. Now we just have to find them...

WORDS: **KAT ARNEY**

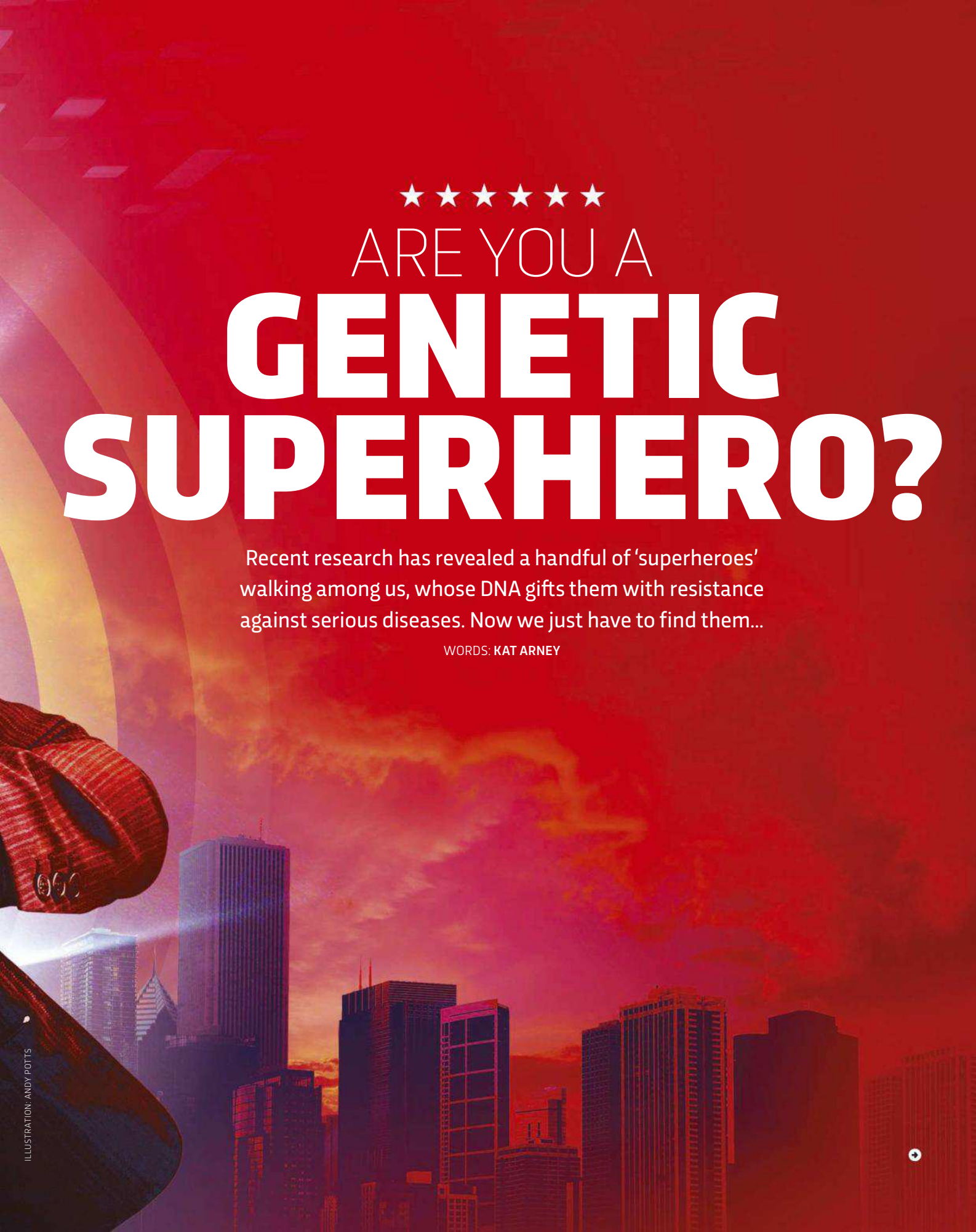


ILLUSTRATION: ANDY POTTS

Superheroes are everywhere right now. Righting wrongs, saving planets and generally punching each other senseless in films, comics and on TV. But just as Clark Kent wanders unrecognised through the world, only turning into Superman when his help is needed, there are genetic superheroes walking among us, and in most cases they're completely unaware of their amazing powers. Only now, by trawling through the DNA of thousands of people, are we discovering their hidden identities.

Dr Cisca Wijmenga and her team at the University of Groningen in the Netherlands never set out to find superheroes. Their project was simply to read the DNA of 250 Dutch families to establish a baseline for the genetic make-up of the country. The team's hope was that as future studies turned up gene variations and mutations linked to disease, they'd be able to tell if the variations were genuinely responsible for causing illness or just part of the underlying DNA of Dutchness.

There are hundreds of healthy Dutch people going about their daily lives, defying the faulty genes within them

Then they found them. Two unlikely heroes, both in their 60s and both carrying two faulty copies of a gene called SERPIN A1 (we usually have two copies of every gene, one from mum, the other from dad). This particular gene normally makes a protein that helps to protect the tubes and air sacs in the lungs. Without it, these structures start to break down, causing serious breathing problems by 30 to 40 years of age. But these two people had made it into their 60s without any severe lung problems.

There was more. Wijmenga points to other examples in the data, such as the 177 people in her study who should, by rights, have a genetic disease called pseudoachondroplasia. The condition leads to unusually short stature and joint pains. But most of the individuals were fine.

The list goes on: Wolfram syndrome (high blood sugar, sight and hearing loss); Wilson's disease (liver problems and psychiatric issues); Niemann-Pick disease (nerve problems and failure to grow properly in childhood) and more. There are hundreds of healthy Dutch people going about their daily lives, defying the faulty genes within them.

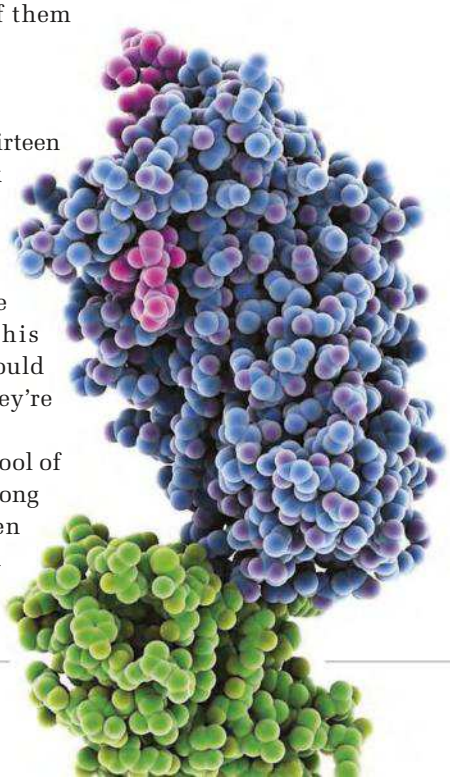
A similar study by Prof David van Heel and his team at Queen Mary University of London came out in March 2016, looking at the DNA of more than 3,200 British Pakistanis living in east London. It revealed 38 people carrying faulty or missing versions of genes linked to serious diseases. Yet the majority were perfectly healthy. In the close-knit Pakistani community, where there are high levels of marriage between blood relatives, there's a greater chance that people will inherit two dodgy copies of a given gene. And although there are higher levels of genetic diseases in this group, they aren't as high as might be expected.

Similarly, a 2015 study on Iceland's population revealed that nearly eight per cent of the island's inhabitants carry two copies of 'bad' versions of disease-causing genes, but many of them are perfectly fine.

REAL SUPERHEROES

Then in April 2016 came the big one. "Thirteen anonymous genetic superheroes walk among us," proclaimed the headlines, reporting on an analysis of more than half a million people's genetic make-up. A team of US researchers known as the Resilience Project discovered that this lucky handful carry mutations that should leave them with serious illnesses, yet they're somehow completely healthy.

Led by Dr Rong Chen at the Icahn School of Medicine at Mount Sinai, New York, along with Dr Eric Schadt and Prof Stephen Friend, the scientists trawled global databases containing information about people's DNA and whether they were



affected by any illnesses. The team focused on mutations responsible for childhood genetic diseases, known as highly penetrant Mendelian diseases, where carrying one or two copies of a faulty gene is enough to cause severe effects.

To start with, Chen spotted around 15,000 individuals who could be heroes, carrying 'bad' mutations in nearly 200 genes linked to more than 160 severe diseases. Further analysis narrowed this down to 300 people, finally ending up with strong evidence for the existence of just 13 who were resilient to a selection of eight genetic conditions.

Three were resistant to cystic fibrosis, a disease affecting the lungs and other organs. Another three were unaffected by gene faults that should have caused major bone abnormalities, known as atelosteogenesis. Two were immune to the impact of mutations in a gene called DHCR7, usually responsible for a developmental disorder known as Smith-Lemli-Opitz syndrome. Another five had genetic resistance against a selection of brain, bone, skin and auto-immune diseases.

HOLDING OUT FOR A HERO

Frustratingly, the identities of these superheroes have to remain a mystery. Due to anonymisation and lack of the correct consent required to re-contact the people in the databases, the Resilience Project wasn't able to track any of these superheroes down for further investigation. This problem has led to some criticisms of the study: there's still a chance that there may have been identity mix-ups along the way (not unusual in such large-scale projects) or that they do actually have mild or more severe forms of the conditions they appear to have evaded.

There may be other issues too. The biggest is the mutation database itself. This is the resource that lists all the genetic faults known to be linked to diseases. This makes Wijmenga sceptical about the powers of many of the individuals she found in her study.

"All of them are disease genes, but some of them are really common in the Dutch population and that makes you wonder if those are true mutations or they just ended up in the database in the past but don't actually cause disease," she says. "For some of these variants, around 90 per cent of the people have the mutant version, which doesn't make sense if it's a real mutation. These things should be rare. So this tells us that the databases aren't that good."

ABOVE: The tests by the Dutch team found some surprising genetic mutations among the population

LEFT: SERPIN A1 is the gene that provides instructions for making a type of protein (blue) that blocks the activity of certain enzymes (green). When there are faults with SERPIN A1, structures in the body can break down

GETTY, SCIENCE PHOTO LIBRARY

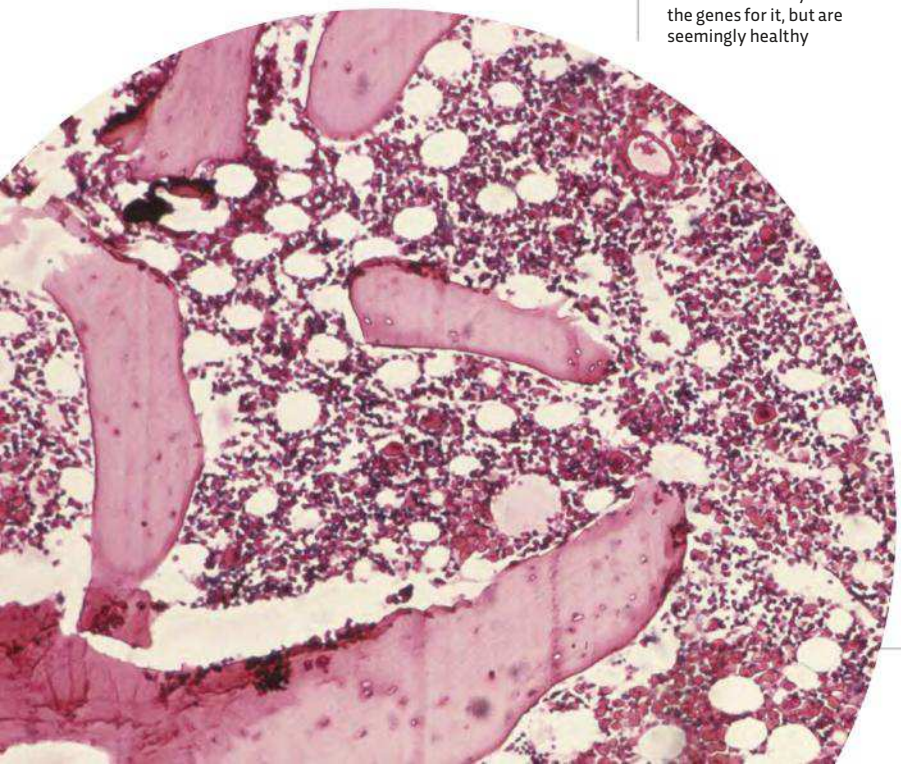
That said, there's still evidence that some superheroes, at least in the genetic sense, are real. And although the identities of those in the Resilience Project's first study will never be known, the next phase promises to bring a new generation of heroes into the spotlight. The plan is to recruit up to a million people from the general population, find the superheroes among them, figure out how they got their powers and harness them for good.

"At this point it still sounds rather ambitious to say things like that," explains Jason Bobe, founding director of Harvard's Personal Genome Project, who's heading up the search. "It's like claiming that you have a platinum record without first writing a hit song, and the challenges of reaching a large number of people are serious."

He's after three types of people to sign up to an interactive app – almost like Facebook for genetics. The app will take them through consent forms and questionnaires, and evolve over time into the most ambitious genetic research project ever undertaken. The first people that Bobe is keen to hear from are those who have reason to believe they're a superhero and are resilient to disease. In some cases, they may have incredibly strong evidence for this.

"For example, we've found a guy who has a really strong family history of early-onset Alzheimer's disease, which is typically fatal within 10 years. He's had a dozen family members die from this disease, which only takes one mutation. He's almost 70 now and figured that he dodged that genetic bullet," explains Bobe. "So he joined a research study and to his surprise he discovered that he actually has the very same mutation that killed so many of his family. Then the question becomes what's so special about this guy? How did he get lucky?"

"With whole genome sequencing, we can generate a lot of data on one person and try to identify the factor that's providing protection"



BELOW: Niemann-Pick disease causes a fatty substance called sphingomyelin to accumulate in the body, as seen in this bone marrow. Some individuals in the Dutch study had the genes for it, but are seemingly healthy

SCIENCE PHOTO LIBRARY X2

Bobe is also keen to attract people who have no reason to believe they're superheroes, just regular genetic Joes with no strong family history of disease, but who are interested in finding out more about their genomes and getting involved in research.

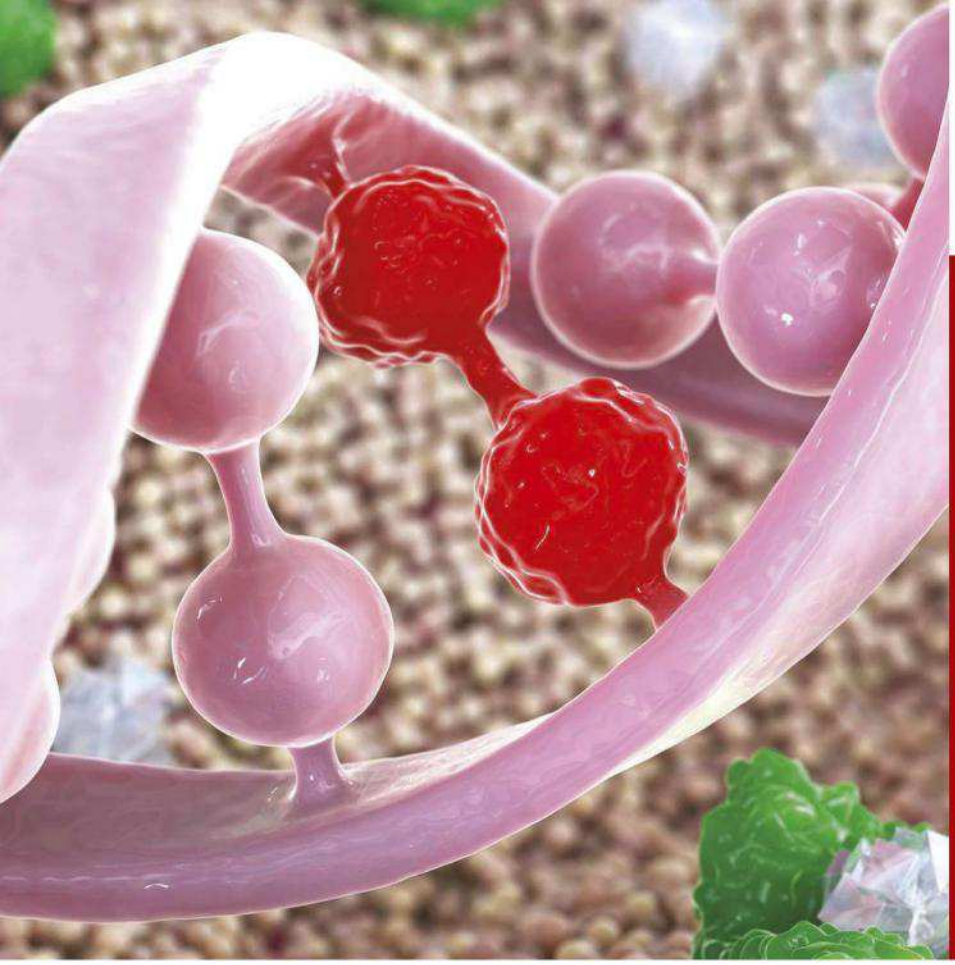
Falling into the third category are people who are affected by a serious Mendelian disease, because they're clearly not resilient.

"If you're actually suffering from the disease there's still a role for you too," Bobe explains. "We'd love to have the participation of people dealing with and managing these diseases, so when we do find somebody who's resilient to cystic fibrosis, for example, we could call upon all those individuals with cystic fibrosis to serve as controls in the decoding."

DECIPHERING THE DATA

It's this part, the decoding, where things get really hard. As the previous studies have shown, superheroes are out there and are relatively easy to find. But the big challenge is working out how they're doing it. Take the example of the man who dodged the Alzheimer's bullet.

"It's what I like to call a smoking airbag, the opposite of the smoking gun," explains Bobe. "This guy has had an airbag in his biology that has gone off and we need to find it, but it's looking for the needle in the haystack. What other genetic or environmental factors in this guy's life have enabled him to escape this



ABOVE: Cystic fibrosis is caused when a child inherits the faulty mutation (red) from both their mum and their dad

HOW DO MUTATIONS WORK?

Mutations can affect the proteins a gene encodes, making it more or less active, or causing disease. For example, if you have a mutation in the BRCA2 gene, you're at a higher risk of breast cancer. Mutations can be inherited or can occur when eggs and sperm are made, or in the fertilised egg. We inherit two copies of every gene, one from each parent, but they're not necessarily the same. Scientists have discovered hundreds of diseases that are caused by inheriting either two copies of a faulty gene (a recessive mutation) or just one (a dominant mutation). These are known as Mendelian diseases, after Gregor Mendel who described the rules of their inheritance. Recessive mutations usually break the gene's function, so people with one copy are unaffected as their remaining healthy gene can compensate. But even inheriting two recessive or one dominant Mendelian disease fault doesn't necessarily mean you'll be severely affected. Genetic superheroes are at the extreme end of this spectrum, carrying 'bad' gene faults but appearing to be healthy.

disease, where in every other case that we've seen it's been fatal.

"Now that we have molecular tools such as whole genome sequencing, we can generate a lot of data on this one person and try to identify the factor that's providing protection. Because if we can identify something like a protective mutation that's actually fending off this heritable disease, then we can identify either preventive strategies or maybe develop new therapies."

The environment may also play a role in determining whether someone succumbs to the effects of a mutation or not. That could cover anything from a person's diet and lifestyle to the womb where they grew into a baby. It's this aspect that most excites Wijmenga.

"In the end there are still people running around with these mutations but still have no disease," she says. "I think if we found out that this is environmental, then that's even better. If you can find out what those environmental factors are, you have much better ways to treat people with 'bad' genes. It is much harder to change your genetics than your environment."

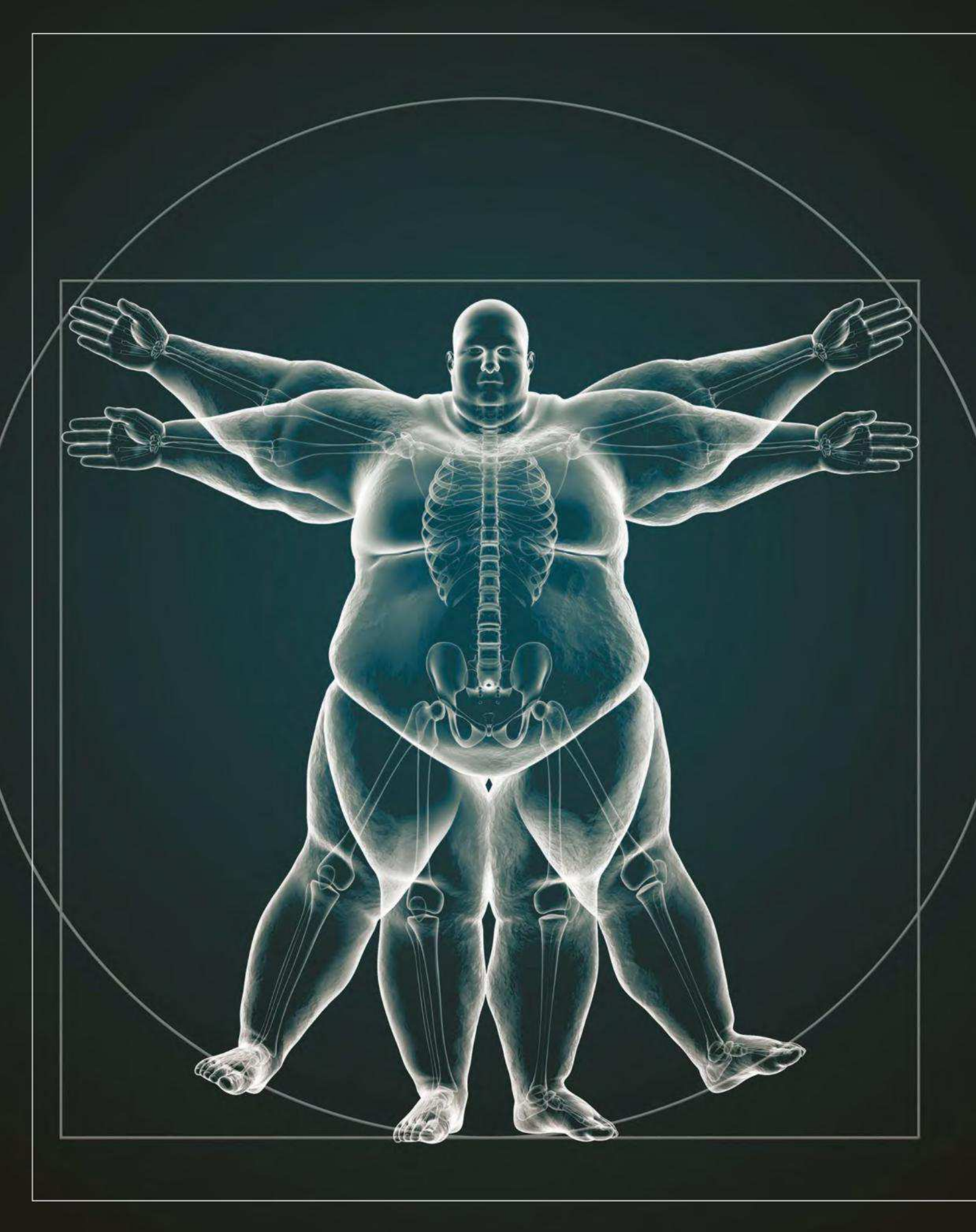
Whether it's nature, nurture or a combination of the two, the existence of genetic superheroes tells us that strictly Mendelian ideas about one gene fault always leading to one disease are far too simplistic. Now we're starting to rifle through the genes of the fit and well, we're finding all kinds of surprises. For a start, we need to start viewing people who carry genes for 'pure' Mendelian diseases as existing along a spectrum, ranging from severely affected at one end to superheroes at the other. And in fact, everyone's a bit mutant, carrying up to 40 'bad' gene faults.

As head of a clinical genetics department, Wijmenga finds this ambiguity challenging. "We're dealing on a daily basis with patients," she says. "We sequence their genome and find a mutation, and we have to predict what we think that means. It's important that we have a much better understanding of our genome and when a mutation matters and when it doesn't. In the past we had this kind of black-and-white idea but now there are all shades of grey. It's an interesting time to be a geneticist, I would say!"

HERO HUNT

The Resilience Project is keen to hear from you if you think that you are resilient to disease. Find out more at resilienceproject.com

Kat Arney is an author and broadcaster who presents *The Naked Scientists* on BBC Radio 5 Live. Her latest book is *How to Code a Human*.



ARE MY GENES TO BLAME IF MY JEANS DON'T FIT?

IN THE UK, 64 PER CENT OF ADULTS ARE OVERWEIGHT OR OBESE. MANY EXPERTS WARN WE ARE FACING A CRISIS. BUT IS THE SOLUTION MORE COMPLICATED THAN 'EATING LESS AND MOVING MORE'?

WORDS: **GILES YEO**

GETTY

Recently, a small supermarket opened at the hospital where I work. It was one of those places that primarily sells convenience food and drink. I was there one day getting a sandwich for lunch, standing in line behind a nurse who had a salad and a yoghurt clutched in her hand. This nurse had clearly started her foraging expedition with the best will in the world, and if the cash till had been right there, she'd have made it out of the shop with an undeniably healthy lunch. However, as the line snaked inexorably towards the checkout, so began the obstacle course of chocolates, sweets, crisps and other temptations that are located, as is typical, close to the tills. The nurse looked longingly at every treat but managed to shuffle past each time. This must have happened 10 or more times. In my head, I was cheering her on: "Come on! You can do it!" Finally she made it to the till and, just as her guard dropped, the cashier pounced: "Would you like some freshly baked cookies? Two for one today." And the battle was lost. The nurse walked out with almost 800 extra calories in cookies.

Who's to blame in this scenario? Do we blame the nurse? Do we blame the shop for putting the food by the tills, or the cashier for making the offer? Do we blame the government for not compelling the supermarket to stop putting junk food by the tills? Should we be throwing stones at all?

Since time immemorial, the control of food intake and body weight has been thought to be simply an issue of self-control and willpower. Gluttony is, after all, one of the seven deadly sins. So as obesity has become an increasing public health problem, reaching epidemic proportions in most developed and emerging economies, society in turn blames the overweight and obese for a lack of moral fortitude.

The prevailing view is that obesity is a simple problem to solve and it's easy to see why. People just have to eat less and move more, and they'll lose weight. It's one of the fundamental laws of physics; you can't magic calories out of nowhere, and likewise you can't magic them away. However, this sage piece of advice that your grandmother could have given you is clearly not working as we're getting fatter and fatter.

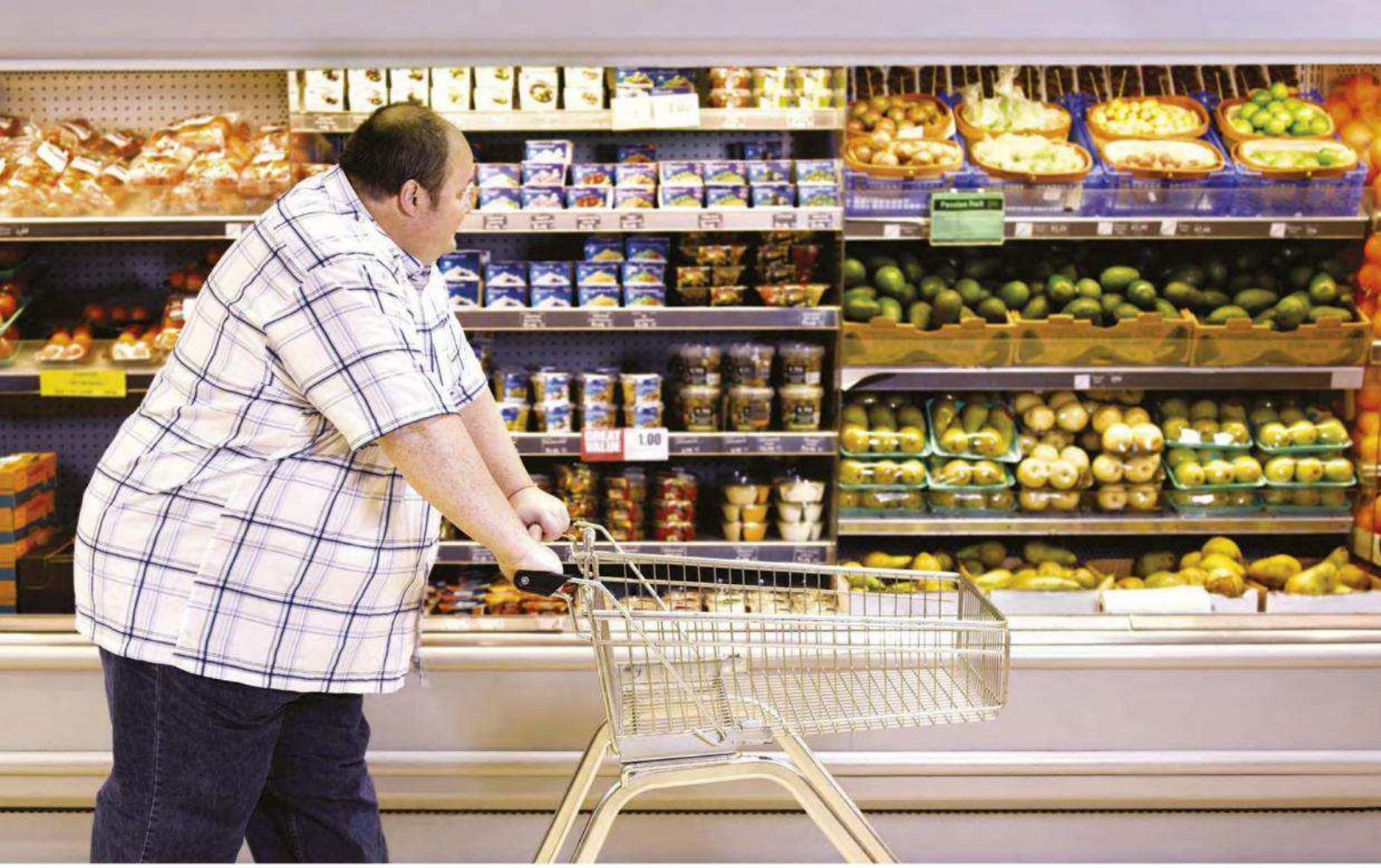
The problem is that we've been focusing on the wrong part of the equation. The question to ask isn't how we've become obese (we do eat too much and move too little), but why some people eat more than others. The answer to this question is incredibly complex, and we're only now beginning to understand the powerful biological and genetic influences on food intake.

It's one of the laws of physics; you can't magic calories out of nowhere, and likewise you can't magic them away

HORMONES AND HERITAGE

We now know that there are hormones that circulate in the blood and signal to the brain, letting it know the nutritional status of the body. Broadly speaking, there are two sources for these signals. The first is hormones secreted from fat, our long-term energy stores, letting our brain know how much we have. This is critical information because how much fat we have is, basically, how long we'll last without food. The second is hormones secreted from our stomach and gut. These are short-term signals that let our brain know what we're currently eating and what we've just eaten. The brain integrates these long- and short-term signals, and influences our feeding behaviour at the next meal. This is our 'fuel sensor'. Yet, while all humans (all mammals in fact) share this fuel sensor, we come in different shapes and sizes. It's becoming clear that variation in body shape and weight is powerfully influenced by genetics.

One of the most invaluable tools in determining the genetic heritability of specific traits is the



Today, we have a huge choice of food available and are bombarded with incentives to make us buy more

GETTY

study of twins. Identical twins are genetic clones, while fraternal (or non-identical) twins share 50 per cent of their genetic material, as you would with any of your siblings. Thus, with the study of enough twins, both identical and fraternal, one could look at any trait that could conceivably have a genetic element, such as eye colour, hair colour, height or weight, and calculate how heritable each trait might be.

As you might imagine, traits such as eye colour and hair colour (peroxide aside) are almost entirely genetically determined with very little environmental influence. In contrast, while a trait like having freckles is clearly genetically influenced, whether, where and how many freckles appear will depend on how much time you spend in the sunshine. What might be surprising is that the heritability of weight is equivalent to that of height. No one would dispute the fact that height is genetically determined: tall parents = tall children. It's also well known that skeletons and written records show that human beings today are inches taller than humans just a century or two ago. Why have we become taller as a species? Change in diet, environment and lifestyle.

It's the same argument with body weight, except that the changes have happened over a shorter period of time. We're now more obese as a species compared to 30 years ago because of changes to our diet, environment and lifestyle. But it does not change the fact that if our parents are overweight, we're much more likely to be overweight.

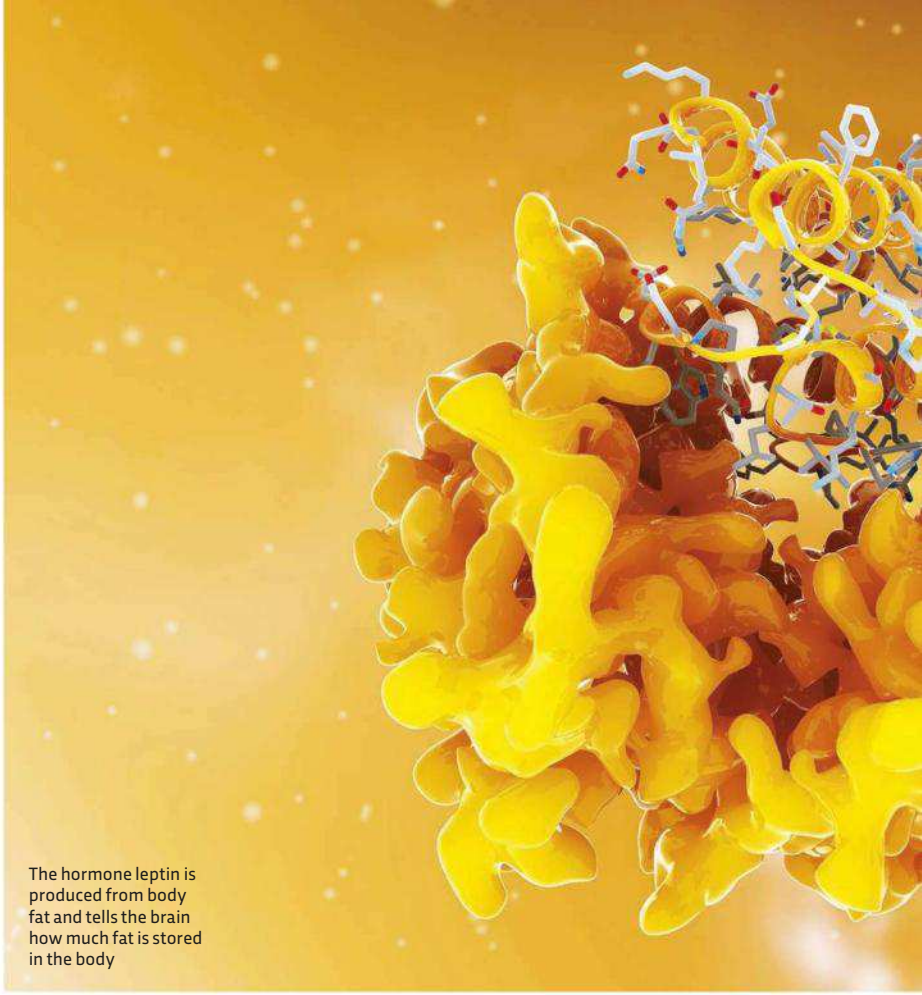
A FAT MAN'S BEST FRIEND

Genetic approaches offer an effective tool for characterising the mechanisms of food intake and body weight control, and allow us to understand how these may become defective in the obese state.

Over the past 20 years, one of the pathways that has been highlighted by genetic studies is the fat-sensing leptin-melanocortin pathway. The hormone leptin is produced from fat and signals to the brain how much fat is stored in the body, while the melanocortin pathway in the brain senses leptin levels and goes on to influence food intake. We know this pathway is critical in the control of food intake, because genetic disruption of either the leptin or the melanocortin pathway results in severe

obesity in humans. When this pathway is disrupted, the brain thinks you have less fat than you actually do, driving you to eat more to gain more fat. This fat-sensing pathway is critical for all mammals, including, as we have recently discovered, dogs.

Labradors, the most popular pet dog breed in the UK and North America, are known to be very food motivated and therefore prone to obesity. We found that nearly a quarter of Labradors have a genetic disruption in the melanocortin pathway that makes them more food motivated and obesity prone than other dogs. The main reason why Labradors are so popular is their lovely disposition and trainability. These traits are also the reason why they're overwhelmingly used as guide dogs for the blind. These dogs are highly trained, often with, you guessed it, food rewards. Nearly 80 per cent of guide dog Labradors carried the genetic mutation, so we think that their disposition and trainability is down to their genetically driven motivation towards food.



The hormone leptin is produced from body fat and tells the brain how much fat is stored in the body

What might be surprising to most people is that the heritability of weight is equivalent to that of height

IT'S ALL IN OUR HEAD

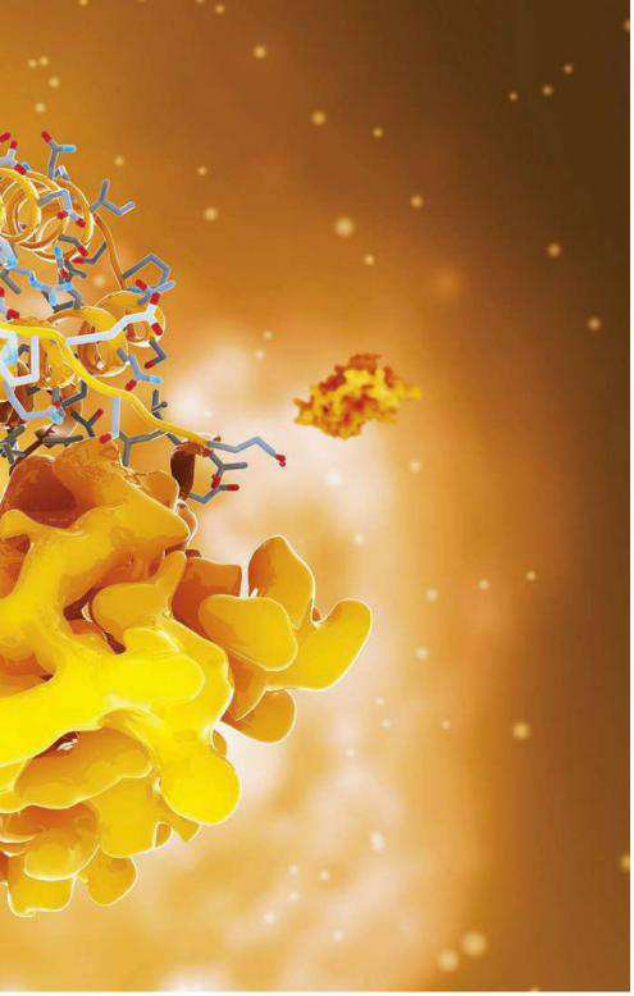
From the human perspective, however, genetic disruption of the melanocortin pathway resulting in severe obesity remains a rare occurrence. The 'common' obesity that currently blights us is more likely to be polygenic in origin, with many subtle genetic variants. Each by itself has an almost imperceptible effect, but together they have a cumulative measurable consequence. We now know of over 100 genes that are linked to obesity. These genes, which include many found in the melanocortin pathway, mostly function within the brain to influence food intake. The evidence tells us that having more risk variants of these genes makes your brain slightly less sensitive to hormones from the fat and gut, with the effect that some of us simply feel a little more hungry all of the time.

Not eating when you're not hungry is really easy. It requires no effort. Have you, however, tried to stop eating when you're still hungry? It's difficult, even for one meal, because it's just not what we're designed to do. We've evolved to eat when there is food, not to stop.

So here's the thing. Thin people aren't morally superior or have willpower made from forged steel, they just feel a little less hungry, so get full up more easily. Equally, obese people aren't morally bereft, lazy or bad. Rather, they're fighting their biology. In essence, an obese brain thinks that you have slightly less fat than you actually do, and you ate slightly less than you actually did the last time round, leading you to eat more at the next meal. But you don't eat twice as much as someone else. You may only eat five per cent more. But a little more every day adds up to a huge difference over a lifetime.

THE 'OOOOOOOOH' FACTOR

Given the importance that eating has on keeping us alive, our brain has evolved strategies to make



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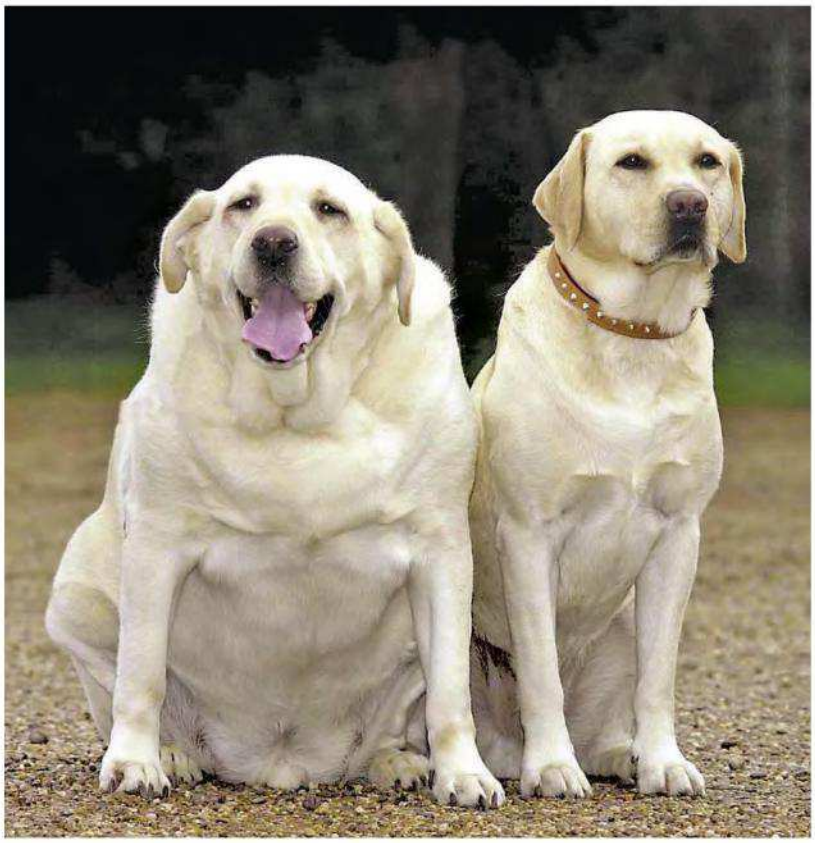

Almost a quarter of Labradors carry a genetic mutation that makes them food-motivated and therefore prone to obesity

sure that it also feels 'good' or rewarding to eat; the 'ooooooooh' factor. This is easily illustrated by the all too familiar 'pudding stomach', despite already feeling full from the previous courses. Certain foods, such as typically energy-dense desserts, trigger the rewarding feeling better than others. This gives us the important motivation to make sure we store all the extra energy we can, ensuring sufficient fuel stores to chase down the next antelope. Having evolved over hundreds of thousands of years to stay alive through multiple famines, any increase in motivation, however small, to continue to search for food was an evolutionary advantage. The rewarding feedback from food that tasted good, and which was presumably not poisonous, was useful in guiding the development and entrainment of our eating behaviour.

There is still the strongly held belief in many quarters that each of us is in full 'executive control' of our eating behaviour, that the environment is responsible for our shape and size, and our genes only have a minimal effect. However, it's crucial to remember that the drive to consume food is one of the most primitive of instincts to promote survival. It's been shaped through millions of years of evolution and has provided living creatures with mechanisms to adapt and respond to times of nutrient scarcity.

Thus, I would argue that to be overweight in our current environment is indeed the natural, even highly evolved, response. The main issue is that the current environment, such as the lunch queue obstacle course faced by the nurse, in which energy-dense treats and stimulatory food cues are ubiquitous, coupled with concurrent changes in lifestyle, is at odds with the millennia of austere surroundings to which we have adapted. This has consequently pushed obesity to become the serious problem it has become today.

I'm fully aware that without this 'obesogenic' environment, most of us would not be overweight or obese; but to deny the central role that our genes have played in our response to this environment is unhelpful as we strive to tackle one of the greatest public health challenges of the 21st century.

BBC TWO

Watch a clip from *Horizon: Why are we getting so fat?* ***bbc.in/2IWElE0***

Giles Yeo is the principal research associate at the MRC Metabolic Diseases Unit, University of Cambridge. He tweets from @gilesyeo.

A CURE FOR BLINDNESS

Viruses aren't always bad – they can be used to deliver healthy genes into cells to slow the progression of inherited eye diseases

WORDS: **SIMON CROMPTON**

Fear of the dark runs deep. According to a survey by the RNIB, more adults in the UK are afraid of losing their sight than they are of developing Alzheimer's, Parkinson's or heart disease.

But that could change as the seemingly miraculous idea of a cure for blindness becomes reality. Recent progress in gene therapy has brought sight to dozens of people who otherwise faced blindness for the rest of their lives.

According to Prof Robin Ali from the Institute of Ophthalmology at University College London, gene therapy is the most advanced new approach to blindness. "It is bringing fantastic improvements in vision," says Ali. "And now there's huge investment from the pharmaceutical industry, which is investigating a range of products."

Gene therapy uses modified viruses to deliver a healthy gene into a cell that has a mutated version of the same gene. The healthy version takes over, and the cell begins to function correctly. The eye is the perfect location for this type of therapy: it is easy to access and is also partially shielded from the immune system, reducing the likelihood of the body's defence mechanisms attacking the virus.

Since 2007, the main focus of gene therapy research has been rare inherited retinal diseases, particularly Leber's congenital amaurosis (LCA) and choroideremia. These disorders cause the breakdown of cells in the retina. Studies in the UK and the US have shown that gene therapy can slow deterioration and even improve vision. While there is some indication that the improvements can wane after a few years, many experts believe that now the principles have been demonstrated, there is momentum to perfect the technique and develop it for more common conditions.

The problem is that while scientists know the genes responsible for conditions such as LCA and choroideremia, they do not know the genes contributing to age-related macular degeneration, or to the majority of other eye conditions. The challenge is to find the genes responsible.

A more experimental approach to gene therapy called optogenetics is being investigated by researchers in Manchester, Oxford, Paris and Dallas. This has the spectacular potential to help all blindness caused by damage to light-sensitive rods and cones. In experiments on mice with damaged retinas, researchers at Manchester University used viruses to inject the gene that codes for the eye's light-detecting pigment (rhodopsin) into the cells behind the retina. After treatment, previously blind mice could judge the size of objects and discriminate black and white bars. The researchers hope to start trials in humans soon.

Simon Crompton is the former health editor for The Times and The Daily Telegraph.

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WHAT CAUSES BLINDNESS?

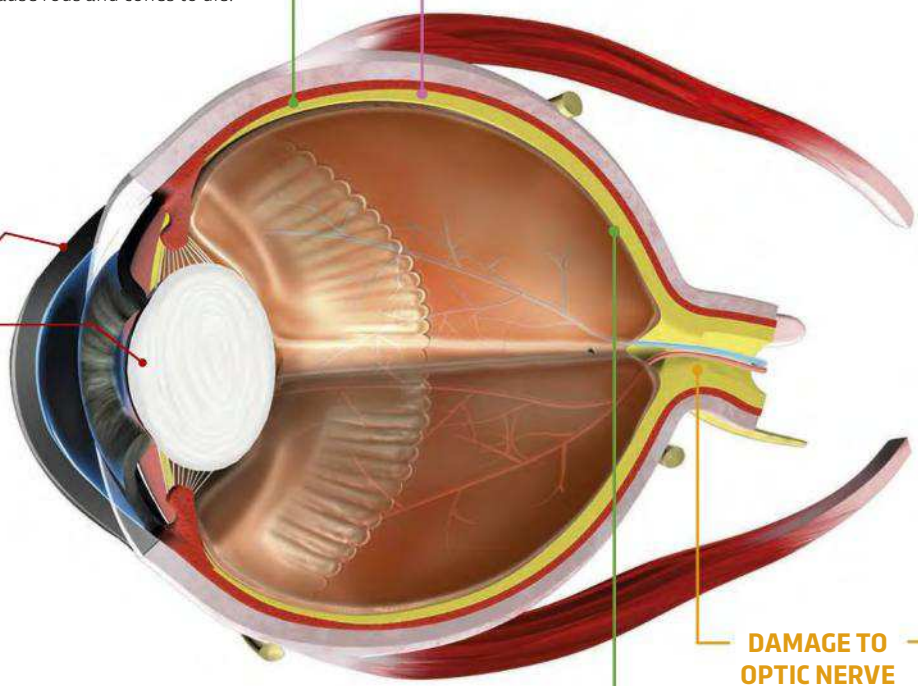
Sight loss isn't the same from person to person

DAMAGE TO RETINAL PIGMENT EPITHELIUM

The retinal pigment epithelium is a layer of cells behind the retina that nourishes and maintains photoreceptors. It's attached to a layer filled with blood vessels, the choroid. Damage to the epithelial cells through age-related macular degeneration, for example, can cause rods and cones to die.

RETINAL DISEASES

The retina is the light-sensitive screen of tissue at the very back of the eye. It contains photoreceptor cells called rods and cones. Rods are sensitive to light, dark, shape and movement, while cones are sensitive to colour. Many retinal diseases, including retinitis pigmentosa, damage or destroy the rods and cones.



PROBLEMS WITH CORNEA AND LENS

As light comes into the eye, it is focused onto the retina by the cornea at the very front and the lens within. Supporting muscles change the shape of the lens to focus. Deformations of the cornea, lack of focusing power in the lens and a distorted eyeball can all cause refractive errors that make up more than 50 per cent of cases of partial sight loss or blindness.

DAMAGE TO OPTIC NERVE

Nerves in the retina carry impulses from photosensitive cells to the brain via the optic nerve. Around 1.2 million nerve fibres from the retina converge to form this nerve. Glaucoma, a group of diseases often associated with increased pressure in the eyeball, can damage the optic nerve and cause blindness if left untreated.

MACULAR DEGENERATION

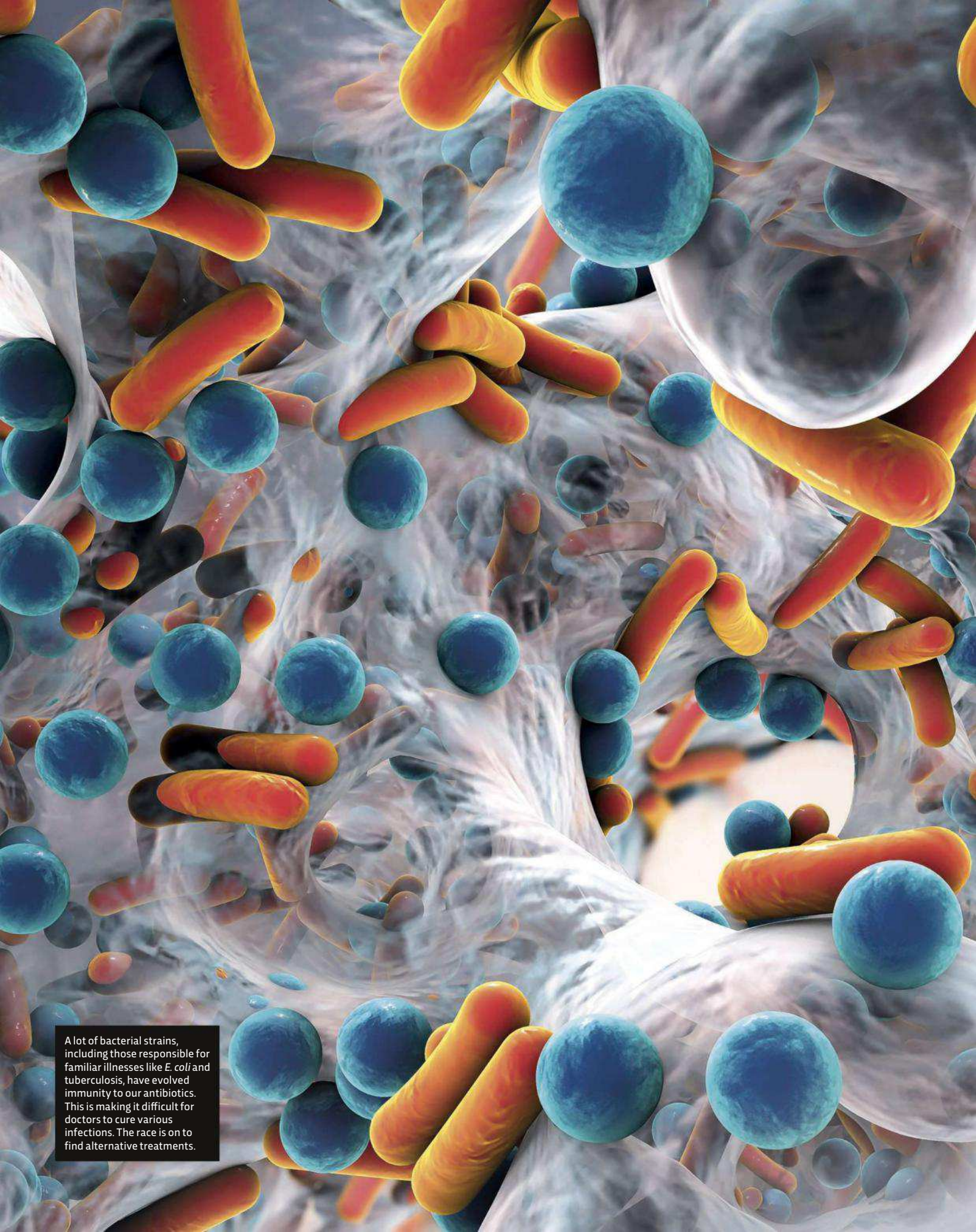
The macula is the central area of the retina where vision is normally sharpest. At its centre is an area called the fovea which has the highest concentration of cones and is responsible for high-resolution vision. Macular degeneration causes the photosensitive cells in these vital areas to deteriorate.

Macular degeneration

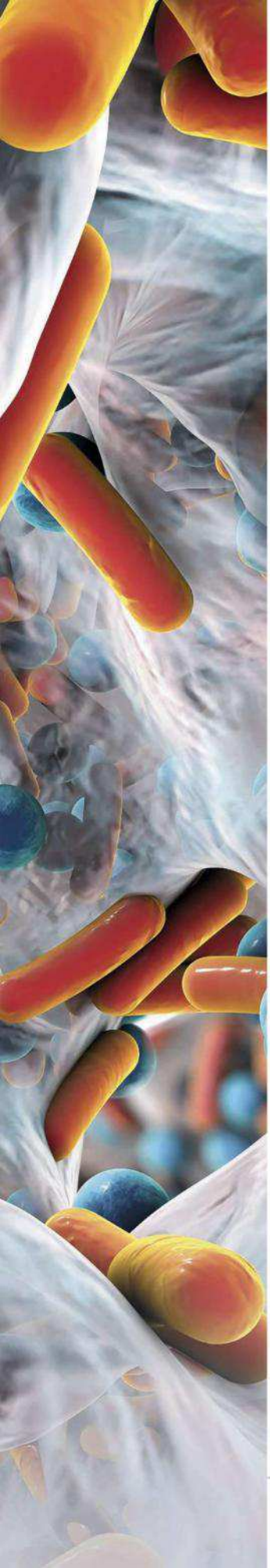
Refractive errors

Glaucoma

Retinitis pigmentosa



A lot of bacterial strains, including those responsible for familiar illnesses like *E. coli* and tuberculosis, have evolved immunity to our antibiotics. This is making it difficult for doctors to cure various infections. The race is on to find alternative treatments.



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THE BATTLE TO BEAT THE SUPERBUGS

Antibiotic resistance is one of the greatest threats to humankind. Genetic mutations are morphing bacteria, protecting them from our onslaught of drugs. And, to make matters worse, viruses, fungi and parasites are also developing resistance. So what can we do about it?

WORDS: **TOM IRELAND**

If you're a fan of apocalyptic disaster movies, you'll be familiar with all manner of things that might bring about the fall of civilisation: asteroid strikes, deadly viruses, alien invasions, nuclear armageddon. Perhaps even an outbreak of zombies.

But what about antibiotic resistance? Experts now believe that the spread of drug-resistant bacteria is probably the single greatest threat to society – greater even than the dangers posed by global terrorism, climate change and anything you'll see at the cinema.

There are signs that this 'antibiotic apocalypse' is already upon us: in Europe and the US alone, at least 50,000 people die each year from infections that don't respond to conventional treatment. Antibiotic-resistant bacteria have been found in every country. If current trends continue, all the world's antibiotic medicines could effectively be useless in just a few decades. According to a report by the *Review On Antimicrobial Resistance*, failure to tackle the problem could cause the world's population to fall by almost half a billion by 2050 and cost the global economy $100tr.

WHY ARE ANTIBIOTICS IMPORTANT?

Antibiotics kill or inhibit the growth of bacteria, helping us to treat both minor and serious bacterial infections. They are used in all areas of medicine, including the treatment of skin conditions such as acne, more serious infections like food poisoning, and deadly contagious diseases such as tuberculosis and meningitis. Antibiotics also stop wounds getting infected after an injury or an operation, and help protect people with damaged immune systems, such as patients undergoing cancer treatment or individuals who have recently received an organ transplant.

There are hundreds of different types of antibiotics, from creams to pills to injections, each developed to target different infections caused by different types of bacteria. Since their introduction around 75 years ago, antibiotics have added approximately 20 years to the

average life expectancy across the globe. Life before these wonder drugs was scary – anything that caused an infection could kill you, even a paper cut. Before modern antibiotics, it's believed that around 40 per cent of all deaths were caused by untreated infections.

HOW DO ANTIBIOTICS WORK?

Antibiotics are chemicals that disrupt key processes in bacterial cells. To be safely used as a drug, they must specifically affect bacterial cells without damaging human tissue. The first modern antibacterial, penicillin, was discovered in 1928 by Scottish scientist Alexander Fleming. Produced by a fungus found in mould, penicillin causes the walls of bacterial cells to fail. Human cells do not have these rigid cell walls, so are unaffected by penicillin, and many similar drugs have been developed over the decades.

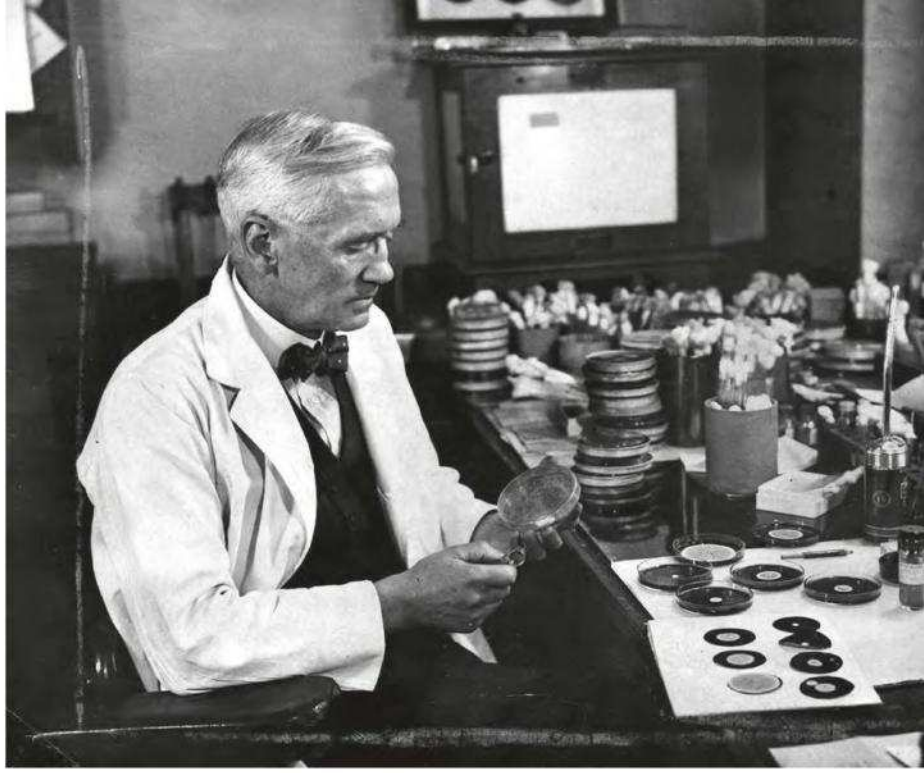
Other antibiotics interfere with processes that are essential for bacteria to grow, such as the production of proteins, DNA, or energy.

HOW DO BACTERIA BECOME RESISTANT?

Although it seems like bacteria are in some way 'learning' how to fight back against us, the development of antibiotic resistance is an inevitable and natural part of bacterial evolution. Each time a bacterium multiplies, it divides into two and copies its DNA. Imperfections in this process mean that in a population of millions, billions or even trillions of multiplying bacterial cells, there are lots of 'mistakes' – mutations – in the DNA of each successive generation.

Owing to the sheer number of variants, over time a tiny proportion of individuals will, by chance, develop a quirk that means they are immune to certain antibiotics. A mutation may, for example, subtly change the structure of a key molecule that the antibiotic targets, rendering it ineffective. Or, it may mean the bacteria start producing a chemical that destroys the antibacterial properties of the drug. In the case of penicillin, many bacteria have evolved to produce chemicals known as beta-lactamase enzymes, which neutralise the drug's effect.

Once it emerges, antibiotic resistance can jump from one species of bacteria to another. Microorganisms naturally exchange genetic material in a process called horizontal gene transfer – either by close contact or by forming a sort of bridge between each other. This helps bacteria shuffle their DNA and 'share' useful genes, but often causes the genes responsible for antibacterial resistance to jump from harmless bacteria into more deadly types.



Alexander Fleming discovered penicillin, which went on to transform the world of medicine

Resistance can also emerge in viruses, fungi and parasites. This is known as anti-microbial resistance, or 'AMR'. Even insects and weeds are developing resistance to the chemicals we use to destroy pests and keep crops healthy.

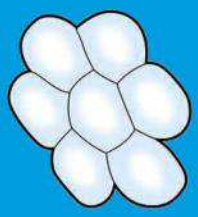
HOW DOES RESISTANCE SPREAD?

Antibiotic resistance becomes a big problem when antibiotics are overused. Using an antibiotic destroys a lot of bacteria in a person's body – both good and bad strains. This means bacteria that are resistant to the antibiotic are free to colonise that space and multiply without competition. This can cause illnesses in the person affected, but also means they will be carrying huge numbers of antibiotic-resistant germs, which are then passed on to other people. Hospitals act like a sort of transport hub for antibiotic-resistant genes: antibiotics are used heavily, concentrating resistance genes in the ward. These are then passed on to staff, other bacteria and patients.

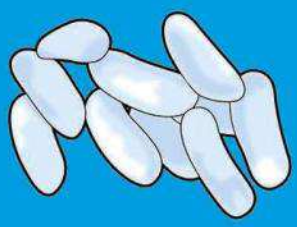
The more often antibiotics are used, the more likely it is that drug-resistant bacteria will come to dominate in any given location. And

THE **9 MOST DANGEROUS** ANTIBIOTIC-RESISTANT BACTERIA

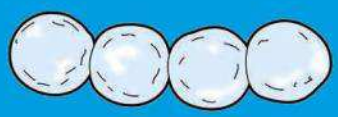
Last year, the World Health Organization released a list of the world's most dangerous bacteria. Nine are classified as being either a high or critically high priority for the development of new antibiotics...



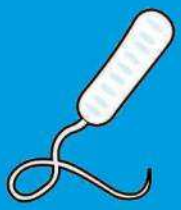
Acinetobacter baumannii
This can cause pneumonia, as well as wound and blood infections in people with compromised immune systems.



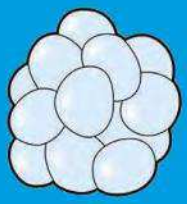
Enterobacteriaceae
Feared as the next superbug, Carbapenem-resistant Enterobacteriaceae kill up to half of patients who get infected by them.



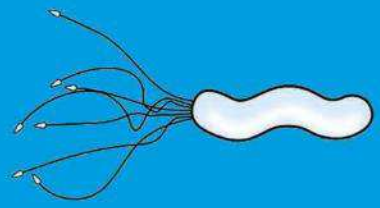
Enterococcus faecium
This bacterium causes urinary tract and blood infections. It's developed six types of resistance to the antibiotic vancomycin.



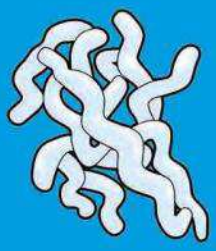
Pseudomonas aeruginosa
Resistant to 'last resort' antibiotics, this bug can cause fatal infections in vulnerable patients.



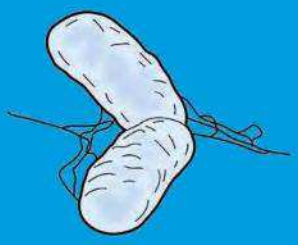
Staphylococcus aureus **(MRSA)**
MRSA lives harmlessly on the skin of around 1 in 30 people, but can cause fatal infections if it goes deeper into the body.



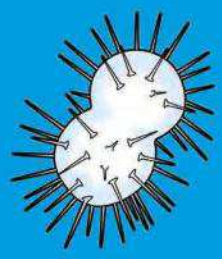
Helicobacter pylori
Often the cause of stomach ulcers, a mutation makes the most common treatment, clarithromycin, ineffective.



Campylobacter spp.
Campylobacter is found in raw meat and causes food poisoning. It is increasingly resistant to fluoroquinolone.



Salmonellae
The many thousands of strains of *Salmonella* can cause illnesses such as typhoid fever and food poisoning.



Neisseria gonorrhoeae
Responsible for the sexually transmitted infection gonorrhoea, antibiotic resistance has been noted since the 1940s.

ILLUSTRATION: ACUTE GRAPHICS

it's not just human medicine that helps spread antibiotic resistance. In some countries, antibiotics are often routinely administered to livestock to boost growth or to prevent infections spreading throughout herds, which means bugs with genes for resistance are passed back to humans via contaminated meat, animal products, or crops fertilised with manure.

Even in countries with excellent hospital hygiene and strict regulations, people and goods from places with poor antibiotic practices are only a short plane flight away.

WHAT IF ANTIBIOTICS STOPPED WORKING?

First, deaths from bacterial infections like tuberculosis and meningitis would undoubtedly rise. Infections that we don't currently think of as deadly would also start to cause serious illnesses and deaths. Even trivial conditions like abscesses or spots would become difficult to treat.

But the effect on healthcare would be even more profound. Each year, billions of operations are carried out around the world, and almost all of them require antibiotics to prevent

WHAT WE STILL DON'T KNOW

1. HOW LONG DO WE HAVE?
As the development of antibiotic resistance is based on chance mutations and random transfer of genetic material, it's hard to predict when and where resistance will emerge, and how much time we have left to find solutions. However, new tools are being deployed to help identify and monitor 'hotspots' of resistance around the world.

2. CAN WE TACKLE IT GLOBALLY?
In many ways, our efforts to curb antibiotic resistance have parallels with climate change: the most advanced efforts in one country are worth nothing if other countries continue as they are. The Western world has made significant progress, but telling developing or poorer nations that they now cannot use antibiotics is not going to be easy.

3. WHEN WILL WE HAVE NEW DRUGS?
It's unclear how successful research into new antibiotics, and new strategies for extending the life of existing antibiotics, will actually be. New drugs can take decades to be proven to be safe for widespread use, and cost millions of dollars to develop. After all that research, bacteria may evolve methods to bypass these new systems anyway.

Without antibiotics, even routine operations would become incredibly risky

infections during and after the procedure. One in four births in England is by caesarian, where antibiotics protect mum and baby.

Without antibiotics, the risk of dying from an infection after these procedures might mean they simply aren't worth it. If antibiotics no longer work, we may have to change the way we behave completely.

HOW WORRIED SHOULD WE BE?

Pretty worried! Many bacteria strains have acquired resistance to more than one type of antibiotic. These 'multi-drug resistant' (MDR) organisms or 'superbugs', are already putting a strain on healthcare systems.

Prof Dame Sally Davies, the UK's chief medical officer, said recently that the golden era of ever-increasing life expectancy may soon give way to an era where mortality rates start to increase. She told a government inquiry on antibiotic resistance that she was far more worried about "dying in an operating theatre during a routine operation" than climate change. Hospitals are struggling to rid wards of multi-drug resistant bacteria such as MRSA, while extensively drug-resistant tuberculosis has now been identified in 100 countries, causing over 200,000 deaths each year. In *E. coli* bacteria, a common cause of food poisoning, resistance to antibiotics is now so widespread that conventional treatment is ineffective in more than half of patients.

And strains of bacteria have been found that are resistant to our 'last resort' antibiotics. Treating patients who have these dangerous bacteria is difficult, hazardous and expensive.

Experts have predicted that, if trends continue, existing antibiotics could be almost useless in as little as 20 years.

CAN'T WE JUST DEVELOP NEW ANTIBIOTICS?

For decades, resistance was relatively rare and the pharmaceutical industry was constantly making new types

MRSA colonies grown on an agar plate in a lab

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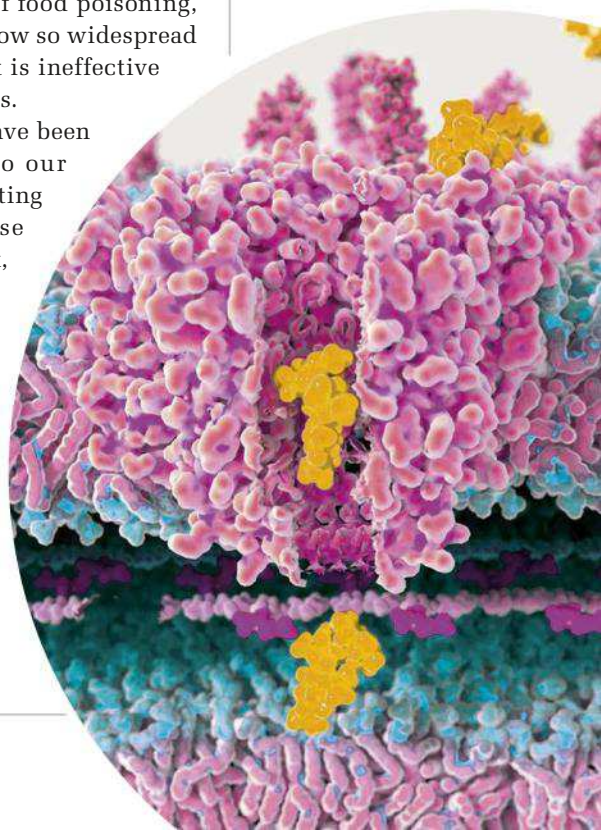


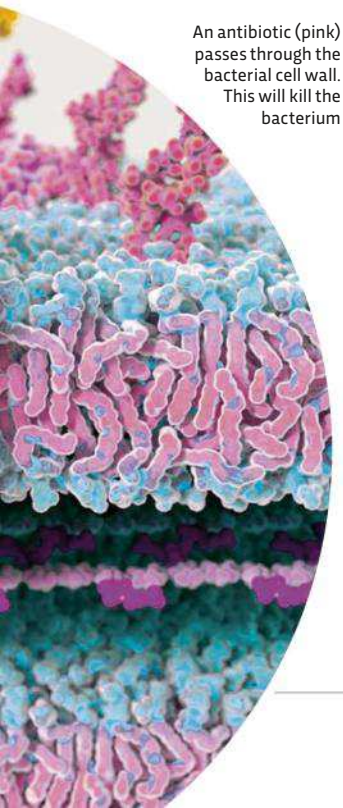
of antibiotics. But by the 1990s, drug companies were starting to run out of new ways to kill bacteria that didn't involve harming human cells. Many efforts to find new drugs resulted in compounds that were similar to existing antibiotics, and so resistance to these developed quickly, too. Most of the antibiotics used around the world today are virtually the same as ones developed 30 years ago.

The biggest problem now is money. It can cost anywhere between $500m and $2bn to discover a new drug and bring it to market, yet these new antibiotics will either be saved for use as a last resort or will become useless when resistance to them develops. This means there is little incentive for pharmaceutical companies to focus their efforts in this area.

But there is some good news: scientists at the Scripps Research Institute in the US recently announced that they have modified a common antibiotic, vancomycin, so that it now attacks bacteria in three different ways. The researchers say the drug could be used widely without fear of resistance as it's so unlikely that bacteria could evade three modes of action at once.

Meanwhile, the likes of ethnobotanist Dr Cassandra Quave, from Emory University in Atlanta, Georgia, is scouring the Mediterranean for forgotten herbal remedies that could help tackle antibiotic resistance.

Experts have predicted that, if trends continue, existing antibiotics could be almost useless in as little as 20 years



An antibiotic (pink) passes through the bacterial cell wall. This will kill the bacterium

ARE THERE ALTERNATIVES TO ANTIBIOTICS?

Scientists are starting to combine antibiotics with compounds that disrupt whatever adaptation the resistant bacteria have developed. For example, if a bacterium has started producing a protein that stops an antibiotic entering its membrane, researchers can develop a 'decoy' compound to block that protein. The patient takes a combination of the antibiotic and the decoy, and the antibiotic suddenly works again. Another alternative is a treatment that has been used in Russia and Eastern Europe since the 1940s but for a long time was not taken seriously in the West. Known as phage therapy, it uses viruses to hijack bacteria and destroy them from the inside. While it may sound dangerous, the viruses used naturally attack bacteria and bacteria only.

Other potential avenues for research include drugs that help the immune system to identify and attack bacteria, the use of bioengineered nanoparticles or viruses to bombard bacteria, and the use of probiotic, 'friendly' bacteria to outcompete the nasty ones.

The problem with all of these potential solutions? Bacteria could develop resistance to any of these treatments eventually, too.

WHAT ELSE CAN WE DO?

Due to the ease with which people can travel around the world, containing the spread of antibiotic resistance requires coordinated global action. To ensure the potency of existing antibiotics, their use must be curbed: they must be prescribed only for bacterial infections, in the proper dose, for the right amount of time.

Lots of research is being directed at tests which will allow GPs to quickly diagnose whether an illness requires antibiotics or not. Other research is looking at ways to interfere with how bacteria swap DNA, to try and eliminate the spread of resistance genes between bacteria.

On an individual level, good general hygiene and regular handwashing helps reduce the spread. People are encouraged not to pressure doctors into giving them antibiotics without knowing what is causing their illness.

In short, the whole of society must start to appreciate these valuable drugs more. The more we use them, the less effective they are.

Tom Ireland is a science writer and editor of *The Biologist*. He tweets from @Tom_J_Ireland.

GENETIC GOLDRUSH

Genetic testing is cheaper than ever. Companies are lining up to sell wine, shoes, fitness plans and more – all tailored to your DNA. But just how feasible are their claims?

WORDS: **KAT ARNEY**

In less than two decades, the science of human genomics – studying the genetic makeup of individuals and populations – has changed beyond recognition. The first full human genome sequence took 10 years and cost nearly $3bn to deliver (at 1991 prices). Today you can spit in a tube, pop it in the post, and expect an email to arrive within weeks detailing thousands of variations within your DNA linked to traits, health and heritage, at a fraction of the cost.

Unsurprisingly, enterprising companies have been quick to jump on the genomic bandwagon, offering everything from fitness plans to personalised wine choices based on your genes. But is it really possible to get such detailed information from a glob of your saliva?

The story of direct-to-consumer (DTC) genetic testing really starts in the early 2000s. At this time, relatively little was known about how small differences in DNA sequences between people – known as single nucleotide polymorphisms, or SNPs (pronounced 'snips') – mapped on to disease risk or physical traits such as height, weight or taste preferences.

Nonetheless, companies sprang up offering pricey nutritional advice and supplements based on testing a handful of SNPs. Given the lack of solid scientific evidence linking SNPs to characteristics, these were dismissed by the authorities as being medically unproven and ambiguous.

By the middle of the decade, the gene-testers had started to wise up. Rather than purporting to offer any kind of medical advice or diagnosis, which would lead them to fall foul of regulators such as the US Food and Drug Administration (FDA), they now claimed to provide their SNP tests purely for informational and educational use. By 2009, more than 500 SNPs had been reliably linked to the risk of diseases such

ILLUSTRATION: JAMES OLSTEIN

There's very little hard evidence that a genetically-tailored diet is any more effective than a generic one

as cancer, and this was growing year-on-year. Anyone with a burning biological curiosity and a thousand dollars to spare could now sign up to 'get their genomes done'. Yet despite their growing popularity, when experts analysed the results of these tests they found them to be misleading or even just plain wrong, driven by deceptive marketing rather than sound science.

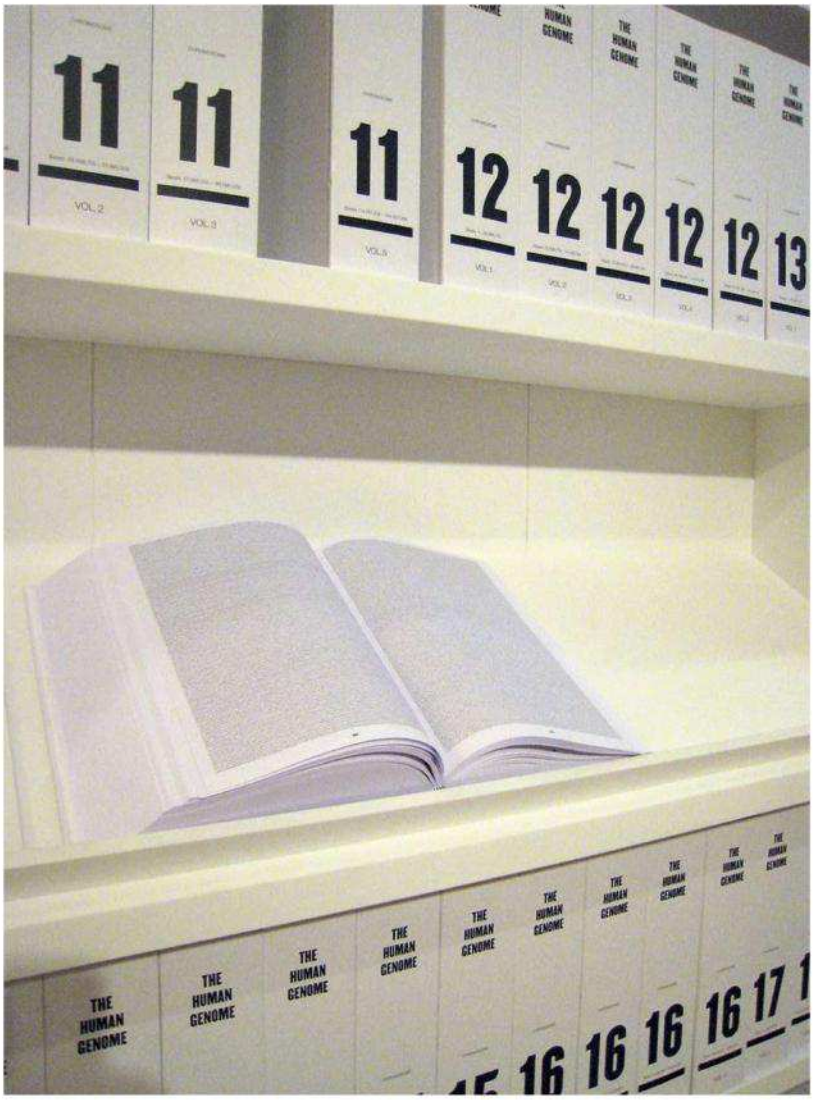
Put off by regulatory crackdowns and a limited consumer base, many of the original SNP-based personalised genetics firms closed down or sold out to larger firms. But there have been a few survivors, and these companies continue to link SNPs to a wide range of disease risks, physical traits and ancestry. And as the pace of technology has accelerated and costs have plummeted, the genetic marketplace is opening up once again.

FAMILY TIES

One of the big boom areas is in genetic ancestry services, with companies offering to find your long-lost genetic relatives and trace your roots around the globe. Some of them even tell romantic stories of ancient tribes, fierce barbarians or sophisticated artists lurking up the ancestral family tree.

It's certainly possible to pin genetic heritage to certain parts of the world, particularly for populations rather than individuals (though even then it's a relatively imprecise science), as well as figuring out what percentage of your genome came from Neanderthals. But many scientists working in the field of human genetics and evolution are less convinced. For example, researchers from the Molecular and Cultural Evolution Laboratory at University College London have investigated and debunked the more dubious claims as little more than "genetic astrology". They argue that the complex patterns of human mating and migration make it tricky to tease apart the tangled genetic threads in each of us with any degree of accuracy.

The other hot topic in DTC testing comes under the broad banner of 'lifestyle'. Companies now offer the chance to 'hack your body' and 'boost your human potential' with all kinds of dietary and fitness advice tailored to your personal combination of certain SNPs. Some recommend combinations of 'genetically selected' vitamins and dietary supplements, while others even offer personalised meals delivered direct to your door. But although these tests all claim to be supported by science – and while it's true that the SNPs they test for have been linked to weight, metabolism or other physical traits in



ABOVE: A printed copy of the human genome fills a whole book

ABOVE RIGHT: A chip containing DNA is loaded into a machine for analysis

large studies – there's actually not very much hard evidence available to suggest that following a genetically-tailored diet and fitness plan is more effective than following a generic one.

In fact, a large randomised controlled trial carried out by scientists at University College London and published in 2015 showed that giving people a weight loss programme alongside information about their personal version of a gene called FTO – which is associated with body weight – made them more likely to think about losing weight, but wasn't any more effective than the programme alone.

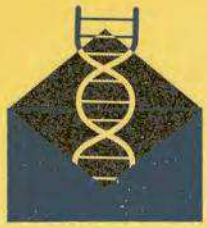
Another study showed no change in behaviour, at least in the short term, for people who were given genetic information about their risk of type 2 diabetes – but there was no increase in worry or anxiety either.

"My feeling is that [DTC tests use] a clever marketing strategy," says Dr Caroline Wright, programme manager for the UK's Deciphering Developmental Disorders study and scientific lead at Genomics England. "The science behind some of these things is tenuous. There are research papers that link variations in DNA with certain attributes, but it doesn't necessarily mean that if you test that particular variant in a particular person it will be predictive for what they like or what they can do."

WELLCOME TRUST, SCIENCE PHOTO LIBRARY. ILLUSTRATIONS: JAMES OLSTEIN

MINING THE GENOME

Personalised genetics companies use two main techniques to quickly and cheaply analyse your DNA. Here's how they compare...

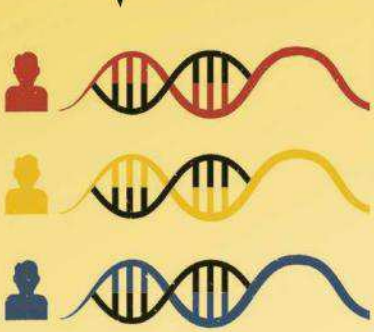


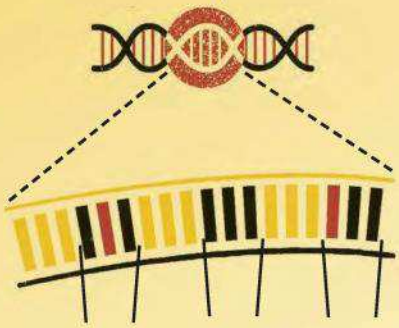
COLLECTION

All that's needed to analyse your DNA is a saliva sample, which can be sent via post to one of the many consumer gene-testing companies.

EXTRACTION

The company extracts and purifies your DNA from cells in the saliva.





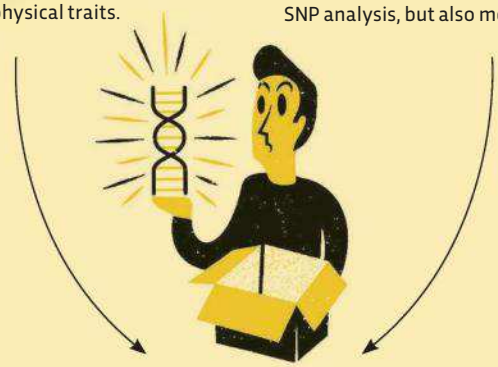
The exome is made up only of exons, which are the coding portions of genes

SNPs

The quickest way to look for DNA variations between people is to find 'single nucleotide polymorphisms' (SNPs). Each SNP corresponds to a difference in a single DNA building block, or nucleotide (the letters A, C, G and T), and some of these SNPs have been linked to particular health and physical traits.

EXOME SEQUENCING

Rather than look at individual DNA letters, exome sequencing involves reading all of the DNA that codes for our 20,000 genes. The exome is only 1.5 per cent of the human genome, but contains much more variation between people than SNPs. This technique is more comprehensive than SNP analysis, but also more expensive.



INFORMATION

Finally, the company will use your DNA variations to give you personalised information about ancestry, family planning, disease risk, fitness, and even food preferences.

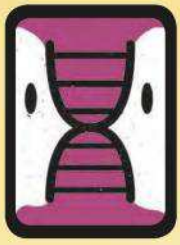
DOWNLOAD

THE GENETIC APP STORE

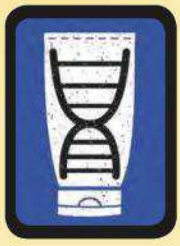
Direct-to-consumer gene-testing companies cover many areas of life. However, the scientific evidence supporting their products may be weak, so buyer beware!

DIET
Some companies are offering personalised diet advice based on a number of genetic markers – a field known as 'nutrigenetics'. The idea is that matching foods to variations in genes that have been linked to obesity, fat metabolism and hunger will bring better weight control. And as a treat, you can buy bespoke beer or fine wines matched to your genes.

SPORT AND FITNESS
As well as matching your diet to your genes, you can tailor your workout, too. From weekend warriors to serious sportspeople, companies offer to analyse genes involved in aerobic (oxygen) capacity, power, endurance, blood pressure and even tendon strength to suggest an ideal training programme, along with a rest and recovery plan.



LOVE AND FAMILY
You can now look for a 'DNA compatible' partner, based on comparing a group of genes involved in the immune system known as the major histocompatibility complex (MHC). Parents can be tested to see if they're likely to produce a child with a genetic condition. And once baby arrives, it's even possible to order a genome test to see what character traits or health risks it's inherited.



SKINCARE
Skincare companies are now offering DNA-based solutions that claim to turn a grotty face into a glowing one. By looking at genes involved in antioxidant protection – which prevents damage from UV rays and chemicals – and the breakdown of the collagen fibres that maintain skin's plumpness, scientists create a personalised anti-ageing serum.

PETS
There's no reason why your pet can't get their genes tested, too! You can now prove whether your pup is pure-breed, or untangle the parentage of a mysterious mutt, as well as looking for health-related DNA variations. Like human DTC tests, you can even get 'wellness advice' about diet, fitness and veterinary care tailor-made for your pet.

Taking advantage of the ever-shrinking cost of DNA sequencing, DTC companies are now moving on from SNPs and taking a deeper look at the human genome. The next step is exome sequencing – reading the entire genetic recipe of all 20,000 genes in the genome, without the 'junk' DNA that lies in-between.

The first firm into the exome marketplace is Helix, backed by DNA technology giant Illumina. Based on the principle of 'sequence once, query often', Helix plans to store customers' exome data and allow them to access it through an app store, with third-party partners offering gene-matched products ranging from health analysis to lifestyle advice.

The first product on offer is Geno 2.0, which is an ancestry analysis package that's produced

ILLUSTRATIONS: JAMES OLSTEIN

23andMe places DNA on a unique genotyping chip to capture information about ancestry and health

23ANDME

in association with National Geographic. Further partners are in the process of signing up, including a range of academic institutions, such as Duke University and the Mayo Clinic. On the less serious side is Vinome, which offers customers regular deliveries of genetically-matched fine wines with "a little science and a lot of fun".

Whether Helix's exome-and-app approach offers anything more than the SNP-based ancestry or diet and wellness tests remains to be seen. The thornier issue will come if Helix offers analysis of genes involved in disease. Not only does this skirt the line with regulatory agencies, which demand that medical tests are only available through a doctor, but it raises important scientific issues too.

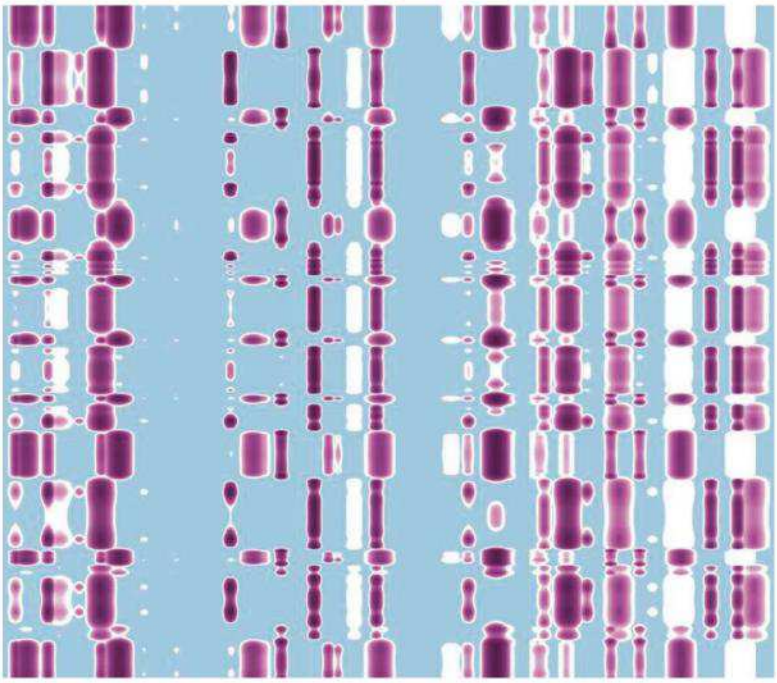
The same issues that have always dogged genetic testing remain, particularly around privacy and consent

"There is no doubt that there is a small but important percentage of people who could hugely benefit from exome sequencing, by discovering that they have a specific genetic variant that causes a disease," explains Wright. "But we know that everybody's genomes are incredibly variable."

She points out that while we have robust information on common SNPs that are linked to disease risk, opening this up to whole exomes is a huge leap into the unknown. Most people have at least some rare or unique genetic variations that look like they ought to be harmful, yet are completely healthy. The big challenge is working out how all the tweaks and changes in someone's genome work together to influence their health.

"We don't have a huge amount of data, and the potential for overdiagnosis and telling someone they have a genetic predisposition [towards a certain disease] is going to be quite tempting," says Wright. "You can tell a story around pretty much anyone's exome, and everyone will have potentially interesting-looking variants. Some of these will genuinely cause disease, but many will not."

The cost of sequencing is rapidly falling – Illumina's NovaSeq machine promises to bring the $100 genome within range. Yet for all the excitement and talk of high-tech apps fuelling the consumer genomic revolution, the same issues remain that have always dogged genetic testing, particularly around privacy, consent and the question of who gets access to the data. Whiling away some idle time in a genetic app store is likely to be a harmless curiosity for most people, and at a time when it's important to



encourage the public to engage with genetics, it seems churlish to raise a note of caution. But wringing data out of your genome could raise more questions than it answers.

"Information about ancestry, fitness and what kind of wine you like might also be mixed in with whether you've got high susceptibility to breast cancer or a gene variant that means you're going to get Alzheimer's disease early in life," says Wright. "Those are quite different types of information, but you'll be able to get it all from your genome. Some of them are fun, and some of them really aren't."

We're seeing the start of a genomic gold rush: in a few years, having your DNA sequenced and rifling through it could be as simple and fun as browsing TV box sets. But it's important to remember that these companies hook curious consumers with promises of genetic insights because they want to make money. This is powerful, personal information, with potentially life-changing consequences, and it's worth handling with care.

Kat Arney is a writer and broadcaster who presents *The Naked Scientists* every week on BBC Radio 5 Live. Her latest book is *How To Code A Human*.

ABOVE: An auto-radiogram showing the order of nucleotide bases in a sample of DNA

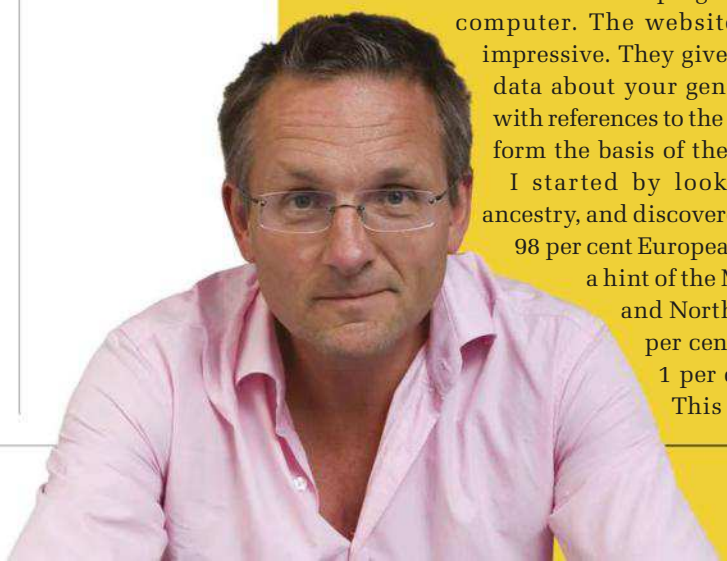
BELOW: In his characteristic guinea pig fashion, Michael Mosley once again volunteers for medical tests

HIGH STREET GENETIC TEST ON TRIAL

Dr Michael Mosley tries out a do-it-yourself DNA test kit and peers into his past and future

A few years ago, I had to donate my spit for a programme I was making for the BBC series *Horizon*. It was for a genetic test provided by 23andMe. The Californian company is named after the 23 pairs of chromosomes in a normal human cell. They certainly make genetic testing very simple. I logged on and paid around £150. You can also buy the kit at a high street chemist. A short while later they sent me a package with instructions. I swabbed my mouth and sent it back. A few weeks later the results pinged up on my computer. The website is rather impressive. They give you lots of data about your genome, along with references to the studies that form the basis of their claims.

I started by looking at my ancestry, and discovered that I am 98 per cent European, with just a hint of the Middle East and North Africa – 1 per cent. I am also 1 per cent Asian. This fits in with



A DNA sequence reveals the presence of ApoE, a genetic marker for Alzheimer's

GETTY, SCIENCE PHOTO LIBRARY, BBC

what I know about my family tree. I had a quick look at inherited conditions and was relieved to see that I am not a carrier of any of the genetic mutations they list, including cystic fibrosis.

I then opened the section on traits. They were very confident I would have straighter hair than average, which is right, but said it was only 28 per cent likely that it would be blonde. I'm not. They told me I'd be tolerant to lactose, which I am, but said my muscle performance suggested I would be a sprinter, which is not true.

I moved on to genetic risk factors, which is undoubtedly the most controversial part of the test. I was particularly interested in my risk of getting Alzheimer's, as I suspect my father was becoming a little bit demented towards the end of his life. There is one gene in particular, ApoE, that is strongly implicated in late-onset Alzheimer's (after the age of 65). No-one knows quite how it works, but ApoE influences the build-up of a protein named amyloid beta in the brain. This protein is found in higher levels in people with Alzheimer's.

The 23andMe test covers three ApoE variants: e2, e3 and e4. It is the e4 variant of the gene that you want to avoid.

According to the website, if you are of European ancestry then one copy of e4 means you have an 18 to 35 per cent of developing Alzheimer's disease by the age of 85. These numbers rise to 51 to 68 per cent if you have two copies of the e4 variant. Fortunately I have two copies of the ApoE e3 variant, which isn't associated with a high risk of developing Alzheimer's.

I went to visit geneticist Dr Ewan Birney, Director of the European Bioinformatics Institute, to see what he thinks about these sort of tests.

"I'm not a fan," he said. "There is a fun side to it, you can use it to trace your ancestry, but I wouldn't recommend it as a way of monitoring my health or your health. There's a risk you might get worried inappropriately, that you will become obsessed about a particular diagnosis that may or may not be right. So this is best handled when you're meeting a clinician who has experience of all of these scenarios to give you good advice."

BBC RADIO 4

Listen to *Inside Science* discussing whether genetic tests are useful and who owns the data
bbc.in/2IY6lHQ

Birney said the tests are quite reliable when it comes to conditions that are affected by a single gene mutation, but not for many common disorders.

"For most common diseases, things like heart disease and Type 2 diabetes, your doctor will know a lot more just by doing some simple tests and finding out about your family history," he said. "The advice you're going to get from your doctor is going to be the same regardless of your genetics, which is don't eat so much, don't smoke, and exercise more."

Dr Michael Mosley presents *Trust Me, I'm A Doctor.*

TURNING THE

A new genetic treatment using stem cells suggests we may be able to reverse the process of ageing

WORDS: **JASON GOODYER**

It has long been known that manipulating certain genes in an organism can slow ageing and extend its lifespan – but the creation of genetic techniques to safely halt or reverse age-related conditions in humans has so far proved elusive.

However, researchers at the Salk Institute of Biology in California have developed a new technique that could be a first step towards the medical world's fabled 'elixir of youth'.

The method, outlined in the journal *Cell*, involved 'switching on' four genes associated with stem cells. It appeared to reverse some signs of ageing in both human skin cells and live mice. The four genes, known as the 'Yamanaka factors', are often used by researchers wanting to turn any type of cell into unspecialised cells known as induced pluripotent stem cells (iPSCs). These cells are capable of dividing indefinitely and becoming any cell type present in the body.

Previous studies found that when cells are made to express Yamanaka genes and turn into iPSCs, they appear younger, having been stripped of the cellular markers of ageing as they revert back to a more fundamental cell type. Yet to induce cells to turn into iPSCs en masse in a live animal would mean many cells cease to function in the way organs need them to, causing organ failure and ultimately death.

However, researchers at the Salk Institute

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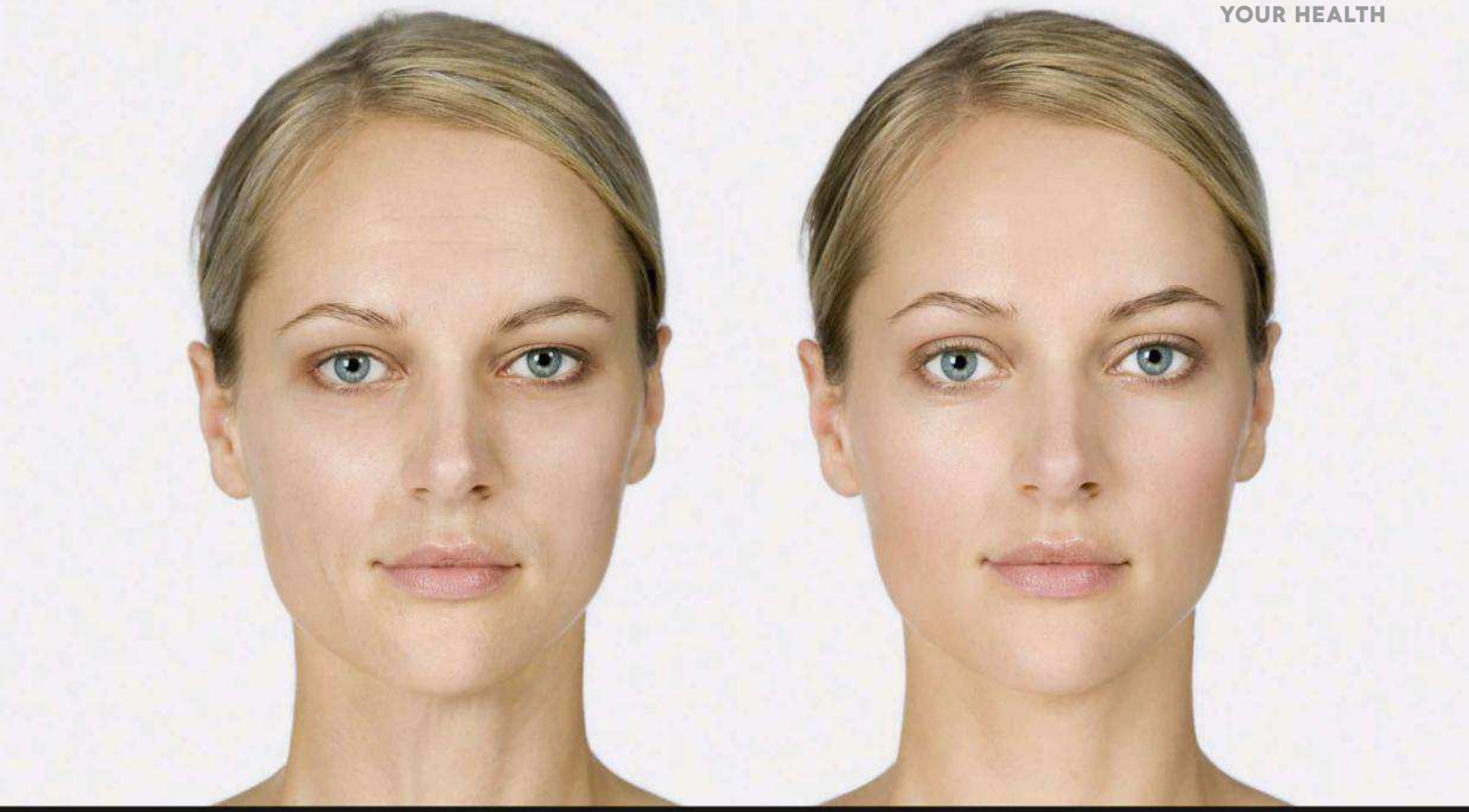


CLOCK BACK

decided to try making cells express the Yamanaka factors cyclically, in bursts. The hope was that the cells would begin to experience some of the age-defying effects of the Yamanaka genes without actually turning into stem cells.

The researchers first tested this idea with skin cells from mice and humans. When they applied their method of cyclically turning on the expression of Yamanaka factors, the cells showed reversal of multiple ageing hallmarks, but did not lose their identity as skin cells.

Next, the researchers used the technique in live mice affected by progeria, a disease that causes accelerated ageing. After inducing the animals to express the genes in short bursts, their cardiovascular performance improved, as did the function of other organs, and the animals lived 30 per cent longer.

Crucially, the mice were not more likely to develop cancer, which is a fundamental drawback of many stem cell-based techniques.

Finally, the scientists turned their efforts to old mice. In these animals, the technique led to an improvement in the ability of the pancreas and muscles to repair themselves, a key process that deteriorates with age.

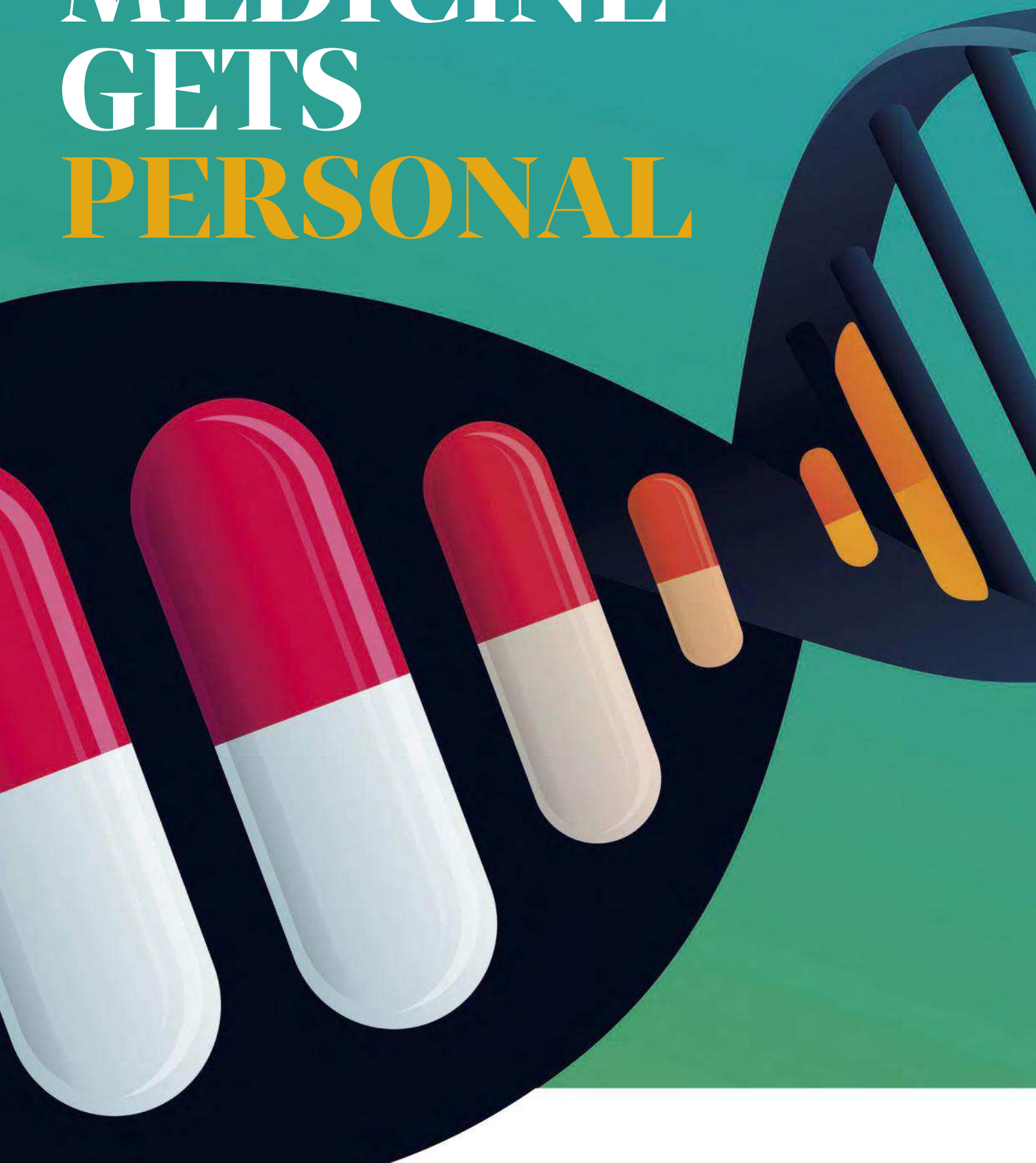
"Obviously, mice are not humans and we know it will be much more complex to rejuvenate a person," says Izpisua Belmonte, one of the study's co-authors. "But this study shows that ageing is a very dynamic and plastic process, and therefore will be more amenable to therapeutic interventions than we previously thought."

Jason Goodyer is the commissioning editor of *BBC Focus* magazine.

BBC RADIO 4

Listen to an episode of FutureProofing on ageing *bbc.in/1XVYMCa*

MEDICINE GETS PERSONAL



Here's a staggering statistic: it is estimated that up to 75 per cent of cancer drugs do not work on the person they are prescribed for. This is because medicines are developed to work on 'the average person' when in fact all of us – and our diseases – are unique

WORDS: **TOM IRELAND**

ILLUSTRATION: TANG YAU HOONG

Modern medicine, for all its wonders, has a rather large blind spot. Although scientific breakthroughs and new miracle treatments are announced on a seemingly daily basis, doctors know that even the most effective drugs in their arsenal won't work for large sections of the population.

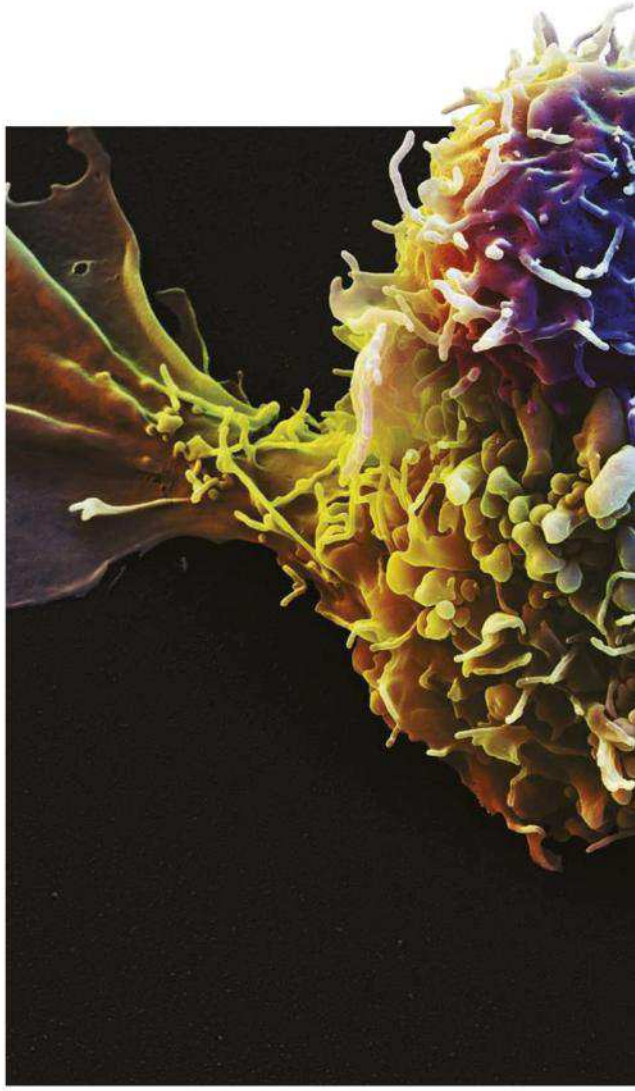
For example, the drugs commonly prescribed to treat disorders like depression, asthma and diabetes are ineffective for around 30-40 per cent of people they are prescribed to. With hard to treat diseases like arthritis, Alzheimer's and cancer, the proportion of the population who see no benefit from a particular treatment rises to 50-75 per cent.

The problem stems from how treatments are developed. Traditionally, a drug is approved for use if it works for a good number of people with similar symptoms in a drug trial – and questions are not asked about those in the study who did not respond to the treatment. When the drug is then released and prescribed to the population en masse, unsurprisingly there are plenty of people – like those in the trial – who discover that the latest 'miracle cure' isn't all that miraculous for them.

This 'one size fits all' system of drug discovery – though it helped uncover the most important medicines of the 20th Century – is now increasingly seen as ineffective, outdated and dangerous. It means medicines are developed to work on 'the average person', when in fact all of us – even our diseases and our responses to drugs – are unique. Not only are many drugs ineffective for large subsections of the population, but they can also cause severe adverse reactions in others.

Thankfully, a completely new approach to medicine is gaining ground. As we learn more about how people differ genetically, medical professionals are tailoring healthcare advice and medical treatment to individuals, rather than populations.

A simple do-it-yourself genetic test can flag the key genes that make people hypersensitive to certain medicines



ABOVE: A cancer cell (yellow/green) being attacked by CAR T-cells that have been taken from a patient's immune system and modified

RIGHT: 23andMe was the first genetic testing kit that UK consumers could buy from a high-street pharmacy, to find out more about traits and ancestry

SCIENCE PHOTO LIBRARY

Personalised medicine (sometimes known as 'precision medicine') uses a patient's genetic data, and other data about their health at the molecular level, to work out the best treatment for that individual person and others with a similar genetic profile.

We tend to think of our genes as determining things such as our height, eye colour, or whether we have a genetic disorder. But the combination of genes we are born with affects our development and health in many subtle ways over the course of our lives. The likelihood of us getting certain diseases as we age, the way we metabolise food, and our reaction to certain drugs are all influenced by the genes we have.

Given what we now know about genes, taking this approach may seem somewhat obvious. But it has only been made possible in the last decade, thanks to the incredible progress that has been made in DNA sequencing technology.

When the human genome was first decoded in 2003, it took over a decade of international collaborative efforts and cost $3bn. Just 15 years later, sequencing a person's genome takes hours rather than years, and can be done for a fraction of the price (see page 62). This means genetic information is more readily available to doctors and researchers developing treatments than ever before.

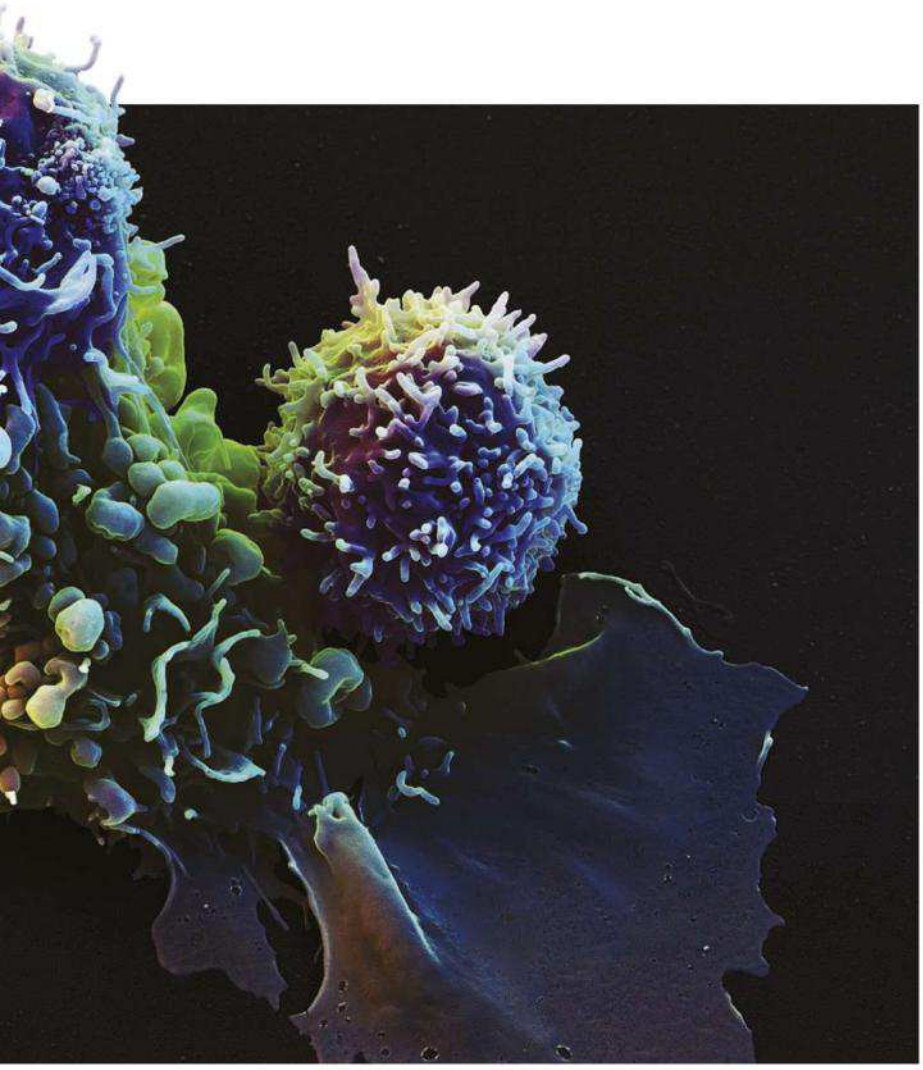
WAR ON CANCER

The area where the new personalised approach to medicine has had the greatest impact, so far, is in oncology, or cancer treatment. The treatment of lung cancer, especially, is seen as a great success story of precision medicine.

For years, doctors were puzzled as to why only around 10 per cent of lung cancer patients responded to a common cancer drug known as TKI (tyrosine kinase inhibitors) that halts a tumour's growth. In the late 2000s, when researchers were able to look at the DNA of patients' tumours, they found the drug actually only worked in people whose cancer cells had one particular mutation in a gene known as EGFR. The mutation causes cells to grow uncontrollably, and TKI blocks this effect, shrinking the tumour. But in patients whose tumours have different genetic origins, a course of treatment with TKI will result in a barrage of nasty side-effects with no chance of success.

Eventually, the different genes at the heart of different lung cancers were revealed, and the entire process for diagnosing lung cancer changed. Cancers are no longer simply classified by where they grow and what they look like under the microscope. Instead they are tested for gene mutations, and treatment options are chosen accordingly. Even when tumours mutate during treatment and develop resistance to gene-specific drugs, doctors can track the genetic change and pick another target.

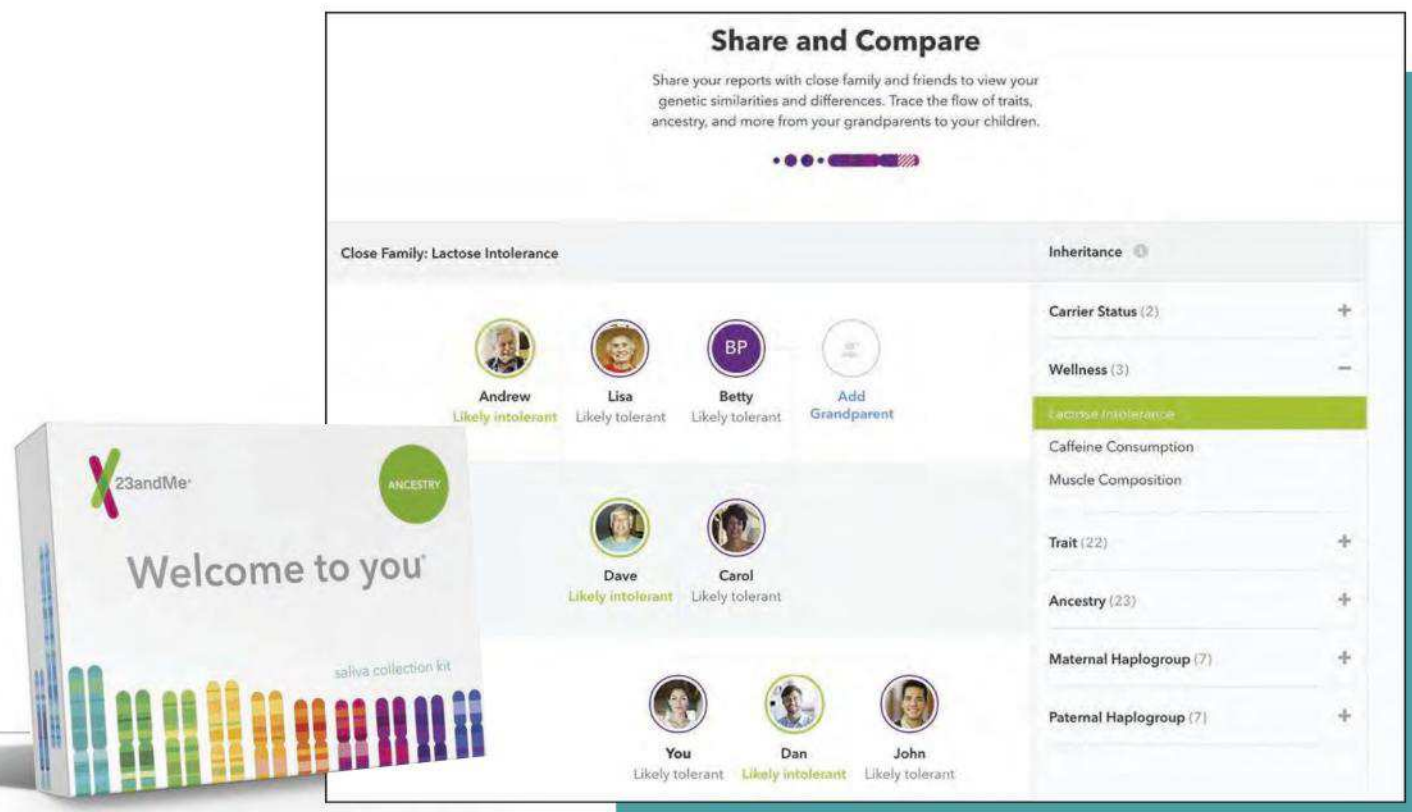
Even more sophisticated personalised cancer treatments are on the horizon, such as immunotherapy, which takes a patient's own immune cells and reprograms them to attack cancer cells. The immune cells, known as CAR T-cells, are extracted from the patient



and genetically modified in the lab so they recognise the exact molecular markers growing on the patient's cancer cells, then injected back in the body to attack the tumour. The US Federal Drug Administration (FDA) approved a form of this treatment in August following impressive results in clinical trials.

Personalised medicine is also making an important contribution to the safety of drugs. Suffering a serious adverse reaction to a medicine may seem rare, but is, incredibly, the fourth leading cause of death in North America, and accounts for as many as 7 per cent of all hospital admissions. Again, the problem is caused by our tendency to try and treat large groups of very different people in the same way.

A simple do-it-yourself genetic test can give a rough idea of potential future health problems (see page 56), while more in-depth tests carried out by professionals can flag up the key genes that make some people hypersensitive to certain medicines, or if someone metabolises drugs so quickly that they need a higher dose. This approach, known as pharmacogenomics, is still far from commonplace in hospitals and GP surgeries, but new software is in



GENOME SEQUENCING

'Whole genome sequencing' involves reading the entire DNA sequence of a person or organism to produce a long string of the letters A, G, T and C – there are around 3.2 billion of these in the human genome. There are also vast sections of our genetic code which have no clear function, so sequencing is often used to reveal only the parts of the genome that contain genes (the 'exome'), or just key sections of variation or interest.

DNA must first be removed and purified from a sample of a person's cells. Chemicals can be used to 'amplify' even tiny amounts of DNA to give scientists more to work with.

To reveal the long sequence of chemical units that make up a person's genome, the purified and amplified DNA is chopped up into many thousands of pieces, which are then separated according to size using electric currents. These fragments form the signature 'bands' seen in an old-fashioned DNA sequence.

For many years, analysis of these bands was painstakingly done by eye, revealing one letter of the DNA sequence at a time. Hugely powerful machines, known as high-throughput sequencers, can now do the same thing in a fraction of the time.

development that will help doctors make prescribing and dosage decisions based on a patient's specific genetic profile. We could one day even see pharmacists checking your genes in-store before handing over your medicines.

DATA-DRIVEN

Personalised medicine is not just about genetics. The medicine of the future will be driven by the generation and interpretation of many types of molecular-level data about individuals, captured with a level of precision never possible before.

"We now have technology that can tell us about your genome, your proteomic profile [protein levels], your metabolic profile and your individual microbiome, in detail, at a cost that is increasingly affordable," says Prof Pieter Cullis, a biochemist at the University of British Columbia and author of several books

The human genome has been printed and bound. The 3.2 billion units of DNA that comprise the genome take up more than 100 books, each filled with 1,000 pages

WENDY DOBING

"We are going to move from sickness-based healthcare to preventative measures, catching these diseases before they happen or while they are still at an early stage"

on personalised medicine. "Gene analysis is informative, but your genes don't change over time and so they can't tell you if you have a particular disease or if your treatment is working. Proteins or metabolites in your blood give us a real-time picture of what your body is trending towards, or whether the drugs you've been given are doing what they are supposed to."

From a simple blood sample, scientists can detect the first chemical clues of a huge range of common diseases (known as 'biomarkers') long before any physical symptoms become apparent. For example, in pancreatic cancer, many patients are only diagnosed when symptoms start to show and the disease is gravely advanced. But the cancer may in fact have been growing asymptomatically for up to 15 years, releasing telltale biomarkers that could be detected with molecular tests.

According to Cullis, a combination of powerful computing, vast databases of genetic and biomedical data, and a greater number of skilled geneticists working in healthcare settings, has the power to truly revolutionise medicine. "We are going to move from sickness-based healthcare to preventative measures," he says, "catching these diseases before they happen or while they are still at an early stage."

Dr Elaine Mardis, a professor of genomics and personalised medicine expert at the Nationwide Children's Hospital in Ohio, calls this approach "precision prevention".

"It's about more regular monitoring and screening for people with high susceptibility to certain diseases. In its most extreme case, people have been found to have disorders that increase their DNA mutation rate or cause defective DNA repair mechanisms, making them likely to develop multiple cancers over their lifetime. They are then placed on a therapy that can hold off the first instance of cancer," says Mardis.

Similar treatments known as 'cancer vaccines' – tailor-made treatments that help people develop 'immunity' to their particular cancer – are currently in development for a range of different diseases including kidney, oral and ovarian cancers. "That, to me, is precision oncology at its finest," says Mardis.

BEYOND CANCER

Personalised medicine is starting to have an impact in many other areas of disease too. In 2016, researchers from the Wellcome Trust Sanger Institute revealed that the most common and dangerous form of leukaemia is actually 11 distinct diseases that each respond very differently to treatment.

In HIV and hepatitis C patients, genomic data taken from both the patient and their viruses can help doctors decide on a drug combination that targets the specific strain of the disease and is less likely to cause side effects in that person. This is important because unpleasant side effects can cause some patients to stop taking their medicines. In Canada, this two-pronged approach reduced death rates from HIV by as much as 90 per cent.

And in Alzheimer's – a disease that is notoriously difficult to treat – genetic analysis is revealing subtypes of the disease that are more likely to respond to certain treatments. Plus, doctors can initiate treatment earlier thanks to the subtle chemical clues that confirm the disease before symptoms are obvious.

But despite all this exciting research, and some remarkable successes, the fact remains that few patients entering the healthcare system in the UK will have access to the specialist biomolecular analysis required to personalise their treatment. Outside of oncology departments, large health systems like the NHS are not yet set up to gather and analyse biomolecular data for every patient. Personalised medicine is too often used as a last resort, or for the lucky few patients selected for clinical trials. The proportion of the population who have had their genome sequenced is tiny.

Visits to the doctor could be replaced by updates from ‘molecular counsellors’ who track health levels

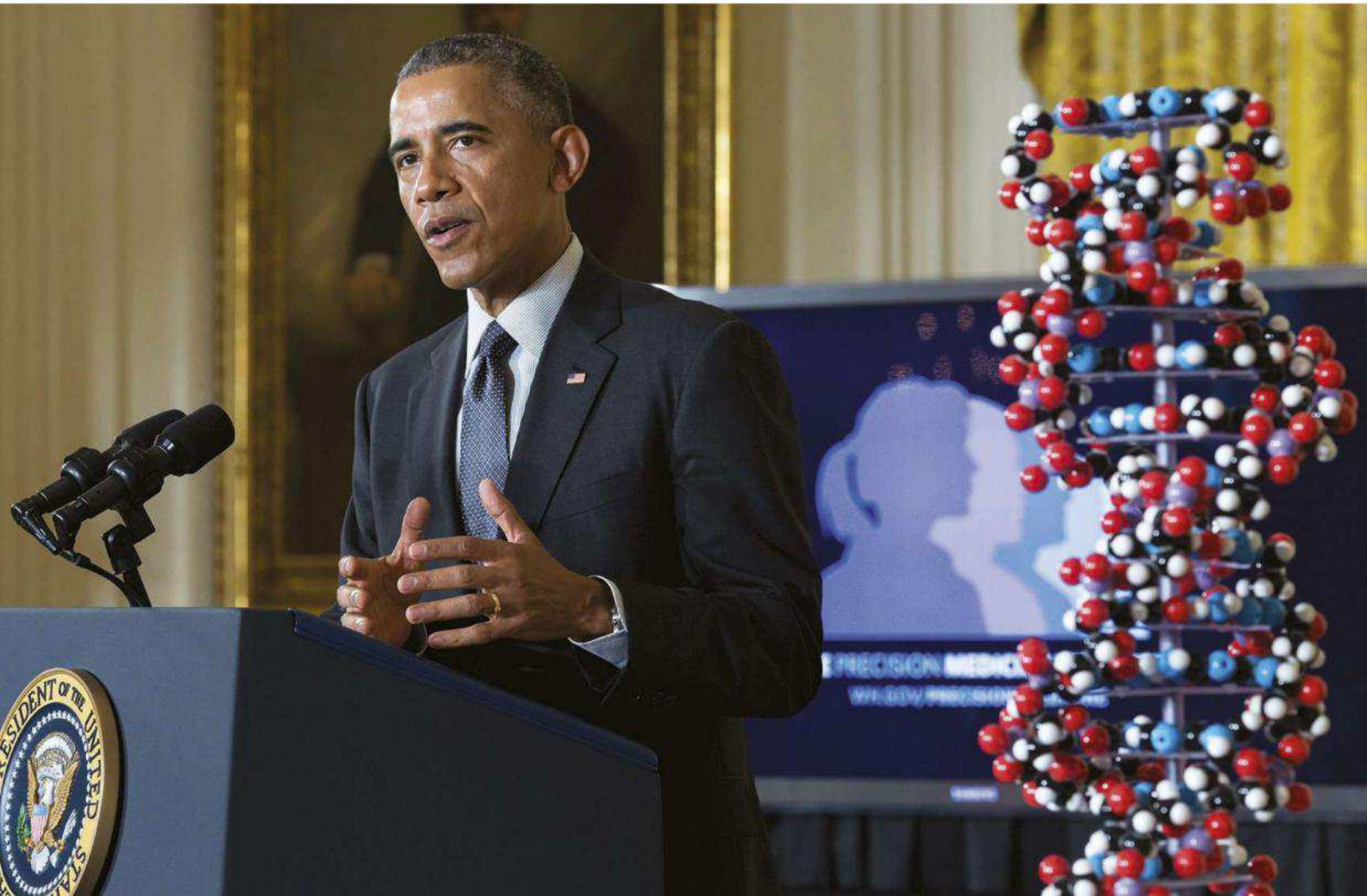
This is starting to change, however. In the UK, the 100,000 Genomes Project has begun sequencing genomes from around 70,000 people with cancer or a rare disease, plus their families, and in 2016 the NHS published its Personalised Medicine Strategy to help drive the adoption of precision approaches in more areas of the health service.

In the US, the world’s largest precision medicine data drive was announced by Barack Obama in 2015. It aims to enrol and sequence genetic data from one million volunteers by 2020. According to Cullis, around 40 per cent of drugs approved in the US in 2016 were ‘personalised’ in some way – meaning the treatment comes with a ‘companion genetic test’ to ensure it is precisely targeted. “In cancer the shift is already happening… companies will genome sequence a tumour and decide the best treatment for you,” says Cullis.

But adopting personalised medicine across all areas of healthcare will require major reforms in how services are staffed and structured.

“A large emphasis of personalised medicine is on preventative medicine and treatment, and healthcare systems have never paid for that before,” says Cullis. “It will be a huge shift and will require a lot of people who are not just doctors but trained in biomolecular analysis. The initial users of this will be people who can afford to pay for it themselves.”

In the next few decades, Cullis foresees that visits to the doctor could be replaced by frequent updates from ‘molecular counsellors’, who track your health levels via regular analysis of the biomarkers in your blood, suggesting treatments



Former US president Barack Obama launched the Precision Medicine Initiative to sequence the DNA of one million volunteers and track their health over many years

THE WHITE HOUSE, GETTY

that are right for your genes. This could be done virtually, with patients uploading their own blood samples to the internet for analysis, and consultation by Skype.

"Molecular analysis will be so disruptive to doctors," says Cullis. "It will take over the diagnostic and prescription process. The doctor will become your health coach, a person whose job it is to keep you healthy and look out for signs that you need to perhaps go for a hike more often, or change your diet."

So is it time to get your genome sequenced? Perhaps not just yet. Depending on the nature and complexity of the test, the cost of genetic testing can range from around £150 to a couple of thousand pounds.

"I had mine done and I didn't find it all that useful,"says Cullis. "It told me I was likely to be susceptible to infections when I'm young – but I'm not young anymore."

However, as the infrastructure in healthcare systems becomes centred around bioinformatics and genetic medicine, it seems inevitable that the medicine of the future will be based around your genes.

"Genome sequencing is getting cheaper all the time," says Cullis, "You only need to do it once. When the systems are in place, it will provide important information about you every time you see a doctor, for the rest of your life."

Tom Ireland is a science journalist and managing editor at the Royal Society of Biology.

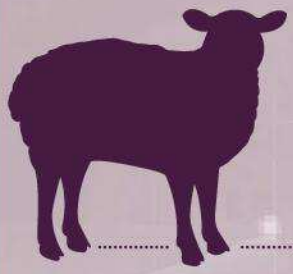
GPs OF THE FUTURE

A trip to see your GP could be very different if the full potential of personalised medicine can be realised. For a start, it may be your doctor that asks to see you...

- To keep track of your health in real time, you regularly upload samples of your blood or other fluids to the internet for remote analysis by experts.
- Assisted by data-crunching algorithms, analysts will alert your doctor at the first sign of the chemical signatures of disease or ill health, long before any symptoms start to show.
- With your molecular data, genetic profile, family history and information about similar patients to hand, a doctor can prescribe a course of treatment suited to your unique circumstances and genes before you even feel ill.
- During treatment, the same molecular metrics of health and disease progression are monitored so that treatment is adjusted according to how you respond.
- If molecular analysis is advanced enough, much of the process of diagnosis and treatment decision could be conducted and communicated remotely via services such as Skype.

BBC RADIO 4

Listen to an episode of *Inside Health* that discusses whether the NHS can deliver the benefits of personalised medicine at *bbc.in/2wxyeA8*



DOLLY THE SHEEP WAS BORN ON 5 JULY 1996 AND WAS THE FIRST MAMMAL TO BE SUCCESSFULLY CLONED FROM AN ADULT CELL

In 2015 it became legal in the UK for a woman carrying faulty DNA in her mitochondria (the 'power packs' of a cell) to use the DNA of another woman, giving rise to ***'three-parent babies'***

SALES OF GM SEED AMOUNTED TO

$15.8bn

IN 2016, EQUIVALENT TO 35% OF GLOBAL COMMERCIAL SEED SALES

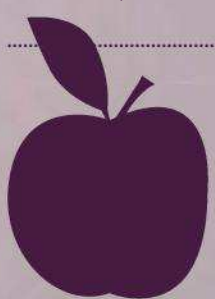
Cloning occurs 'naturally' in nature when asexual organisms reproduce to produce an identical copy of themselves

The USA, Brazil, Argentina, India and Canada were the ***top 5 countries*** cultivating GM crops in terms of area in 2015

EATING GM-FREE FOOD WOULD INCREASE THE AVERAGE FAMILY FOOD BUDGET FROM **$9,462** TO **$12,181** A YEAR

90%

OF THE SOY, COTTON, CORN AND SUGAR BEETS SOLD IN THE US HAVE BEEN GENETICALLY MODIFIED



Apples have been **genetically modified** to reduce bruising and browning by cutting back on the levels of enzymes that cause this

GETTY

THE FUTURE OF GENETICS

Genetic engineering might be a solution to a wide range of problems. It could allow us to feed the hungry, heal the sick and save endangered species from extinction. But all that assumes we understand genetics enough to avoid the dangers posed by meddling with our genetic codes – and that of other life forms. So where do we go from here? What problems should we use the tech to solve? Which species do we save? And who do we bring back from the dead?

WHERE ARE ALL THE CLONES?

It's over 20 years since scientists cloned Dolly the sheep. Since then, various other animals have been cloned. But should we be doing this? And what does the future hold for cloning humans?

WORDS: **HENRY NICHOLLS** AND **HELEN PILCHER**

GETTY

Watch an archived *Horizon* episode about why Dolly the sheep was created
bbc.in/1Tli8j2

Embryologist Bill Ritchie knew that Dolly the sheep would be big news. But looking back to the days after the press got wind of the cloned sheep, he's still amazed by the sensation she caused. "By the Monday morning, the place was full of trucks with dishes sending the news around the world," says Ritchie, then at the Roslin Institute at the University of Edinburgh and one of the researchers behind the creation of Dolly. "All hell had broken loose."

One reporter imagined that Dolly might herald "a scientific explosion comparable to the atom bomb or the Moon rocket or DNA itself". There were accusations that the scientists were playing God. Some envisaged herds of cloned sheep. One commentator even raised the alarming prospect that "any decent college or graduate school student could potentially clone a human being". Others were more positive, seeing cloning as a lifeline for endangered species.

Given the excitement, it's reasonable to ask what happened. Where are all the clones now? What worked and what didn't? Who's still cloning and why? Over 20 years after Dolly, what is her legacy?

"Everyone thought it was going to be so easy," says Ritchie. But it isn't. In the case of Dolly, Ritchie succeeded in creating 277 cloned sheep cells. Of these, only 29 began to divide normally and were implanted into surrogate ewes. There was just one pregnancy that reached term. "It's not a particularly efficient technique," he explains. "I sometimes wonder how it works at all."

But have we learned anything to help us improve this efficiency? "Not a lot," says Ritchie. "It's still a very inefficient process." This fact explains why so many of the applications envisaged for cloning haven't taken off. Take agriculture, for instance. There would be huge interest in copying the most prized individuals in a herd, simultaneously improving the quality and consistency of the animals. But the low success rate of cloning, coupled with concerns over the safety of consuming cloned products, means only the boldest players dare to dabble. In China, the world's largest animal-cloning factory is under construction in the city of Tianjin. BoyaLife's aim is to produce 100,000 high-quality cow embryos with a view to feeding China's growing appetite for beef, eventually scaling up to one million animals a year.

INEFFICIENCIES AND INCENTIVES

The inefficiencies involved also mean that cloning of valuable animals remains a relatively niche activity that's only accessible to the super-rich. In Idaho in the US, for instance, businessman and mule-racing enthusiast Donald Jacklin ploughed some of his wealth into a project to clone a mule. Cloning has also been used to create breeding replicas of castrated racehorses. It's not cheap, but given the astronomical fees that a valuable stud can command there might be a financial incentive. But it remains a niche activity.

So, is there really any point in humanity cloning animals? Should we clone humans? And what does the future hold?

COULD WE CLONE A NEANDERTHAL?

The Neanderthal genome was sequenced in 2010. Meanwhile, new gene-editing tools mean the technical barriers to 'de-extinction' are being overcome. So, technically, yes, we could attempt to clone a Neanderthal. We'd need to introduce Neanderthal DNA into a human stem cell, before finding a human surrogate mother to carry the Neanderthal-esque embryo. But there'd likely be mismatches between mother and embryo that might make the endeavour unfeasible. And, given that the Neanderthal is our closest relative, its cloning would likely be regulated as whole human or reproductive cloning, which in most countries is illegal.

Cloning a Neanderthal might be possible, but would it be ethical?

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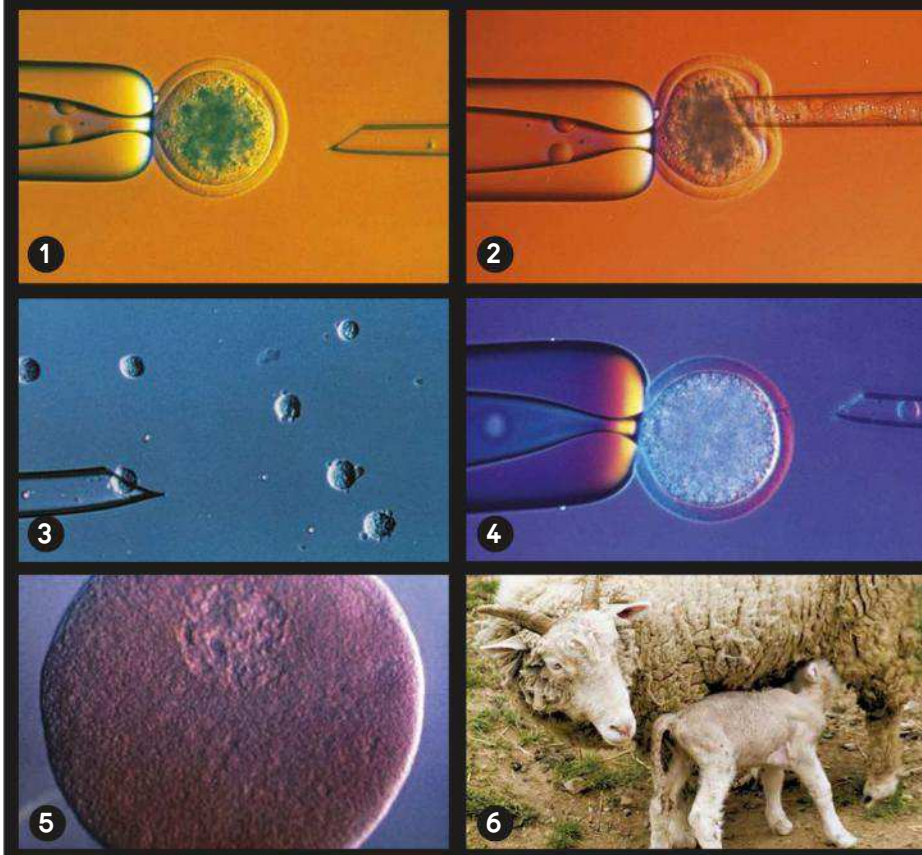


HOW DOES CLONING WORK?

A cell in an early embryo has something akin to a superpower. It can transform into any part of the organism, a skin cell perhaps, a muscle cell, a nerve cell or a blood cell. Before Dolly, everyone assumed that in mammals this process of specialisation, so-called 'differentiation', was irreversible. Dolly proved otherwise.

1. Scientists start with an egg cell.
2. The nucleus (the part of the cell that contains the majority of the genetic material) is removed from the egg cell.
3. A single differentiated cell, in this case an udder cell from an adult donor, is picked up by a tiny needle.
4. The udder cell is injected into the egg cell and a small electrical pulse is used to fuse the nucleus into its new environment and to kick-start cell division.
5. The egg cell and differentiated cell fuse. You can see in this image that the egg cell now has a nucleus (upper centre).
6. The embryo is implanted into the uterus of a surrogate female. She carries the clone to term.

TIMELINE: ANIMALS THAT WERE CLONED

1894

German biologist Hans Driesch takes a two-cell sea urchin from the Bay of Naples and shakes it in a beaker of water. The cells part, giving rise to two identical sea urchins.

1902

Hans Spemann, another German scientist, uses a fine hair from his baby son to split a salamander embryo in two. The result: two amphibians for the price of one.

1952

In the US, Robert Briggs and Thomas King perform a successful nuclear transfer, by moving a nucleus from an embryonic frog cell into an egg cell whose own nucleus had been removed.

1962

Instead of using nuclei from frog embryos, Oxford biologist John Gurdon takes them from adults, to show that a differentiated nucleus still has the power to build an entire animal.

HOW CAN CLONING HELP COMBAT DISEASE?

One of the most valuable applications of cloning has been to improve on existing mouse models of human disease.

"A mouse is not a human," says Angelika Schnieke, a key player in the Dolly project and now chair of livestock biotechnology at the Technische Universitat Munchen in Germany. "A pig is not a human either but its physiology is a lot closer." In the last few years, cloning has been used to create pig models of cystic fibrosis, bowel cancer, diabetes and cardiovascular disease. These are being used to test new medications, imaging technologies and treatment options.

Cloning has also brought us closer to a world in which pig organs could be routinely used in transplantation. By modifying embryonic pig cells and introducing a few human genes, researchers have been able to clone pigs with organs that are less likely to be rejected by the human immune system.

With cloning, it's also possible to think about engineering animals that are resistant to common diseases. In 2014, for instance, Chinese scientists used genetic manipulation plus cloning to create cows that are resistant to the bacterium responsible for mastitis, a condition that causes udder tissue to become painful and inflamed. This research could save farmers billions of dollars in lost revenue to boot. A similar approach could be used to engineer cattle resistant to the parasite that causes sleeping sickness, a major constraint to livestock production in sub-Saharan Africa.

Seoul, South Korea – Professor Woo-Suk Hwang's assistants extract eggs from cow and pig ovaries

More recently, scientists have cloned monkeys. Earlier this year, a Chinese team announced that they had cloned two female long-tailed macaques, Zhong Zhong and Hua Hua, in an attempt to help treat diseases such as cancer, Parkinson's and Alzheimer's. Monkeys are certainly closer replicas of humans than, for example, mice. Indeed, all attempts to treat symptoms that mimic Alzheimer's in mice have not been successful when trialled in humans. But the cost and ethics of breeding monkeys, and other animals, for cloning is an issue.

There could also be environmental benefits of cloning. Researchers at the University of Guelph in Canada have created Enviropigs, animals with a bonus enzyme that means they produce less phosphate in their manure and so are less polluting.

1963

Chinese embryologist Tong Dizhou applies the same technique to fish, though his work, originally published in Chinese, does not receive much attention beyond China.

1996

When it came to making Dolly, of 277 cloned sheep cells only 29 developed into embryos. Dolly was the only one that continued developing after being implanted into a ewe.

2001

Researchers at Texas A&M University create the first cloned pet, using a cell from a brown-and-white tabby cat called Rainbow to make 'CC' (aka 'Copy Cat' and 'Carbon Copy').

2001

Scientists at Advanced Cell Technology in the US are the first to clone an endangered species. Noah the gaur, a species of wild ox native to Asia, dies from dysentry after two days.

2005

Controversial South Korean scientist Hwang Woo-Suk uses the ear cell from an Afghan hound to make Snuppy, the world's first cloned dog. A Labrador acts as surrogate mother.

COULD WE CREATE A WOOLLY MAMMOTH?

Sort of. In South Korea, Japan and the US, three teams are racing to bring back the woolly mammoth. But it won't be exactly the same as the real thing – just an elephant with a sprinkling of mammoth DNA. It'll have long, shaggy fur, thick rolls of insulating body fat and haemoglobin that can ferry oxygen around the body at sub-zero temperatures. So, this will be an animal that looks like a mammoth, but is really an elephant whose DNA has been altered so it can live in the cold. You could call it a 'mammophant' if you like, or an 'elemoth'.

Scientists are also working on bringing back other animals. Back in 2003, European scientists managed to resurrect the Pyrenean ibex (or bucardo), a type of mountain goat that had gone extinct a few years earlier. Sadly, the kid died a few minutes after she was born, so the bucardo was not only the first animal to be brought back from extinction, but also the first to go extinct twice.

Since then, scientists have been refining their methods and developing new 'de-extinction' techniques. In Australia, Prof Michael Archer and colleagues are trying to bring back the gastric-brooding frog, a remarkable animal that nurtured its young in its stomach before burping up fully-formed froglets. So far, the team has produced embryos that 'almost' turn into tadpoles but not quite. The next step is to persuade these embryos to turn into frogs, something that Archer is convinced they will achieve.

Cloned boxer dogs jostle for attention at the Sooam facility in South Korea

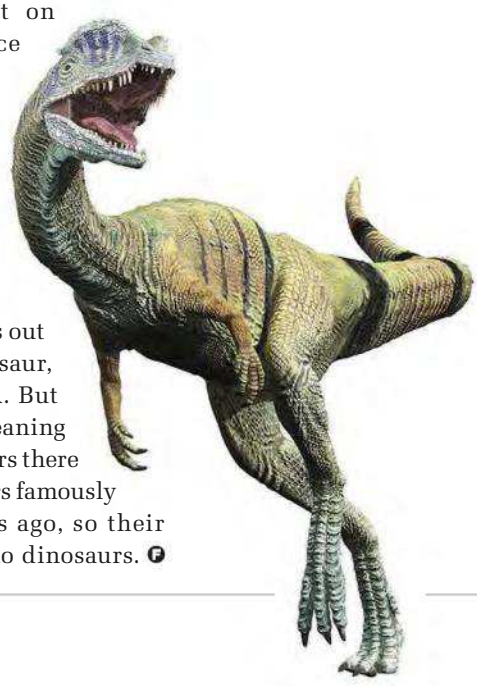
WOULD YOU CLONE YOUR DOG?

The labs at Sooam Biotech Research Foundation in Seoul, South Korea, regularly produce cloned dogs for the Korean National Police Agency and will even clone your pet pooch for around £65,000.

But although the doppelgänger will look like your faithful friend, it'll never be the same. Just as identical twins develop different personalities, physical characteristics and diseases, 'Fido II' will grow into a different dog. Current cloning techniques are unreliable. It can often take more than 100 attempts to clone a healthy animal, and even then conditions in the womb and other environmental factors can have a dramatic effect on the resulting dog's appearance and personality.

COULD WE RESURRECT DINOSAURS?

Sadly, a real-life Jurassic Park is out of the question. To clone a dinosaur, scientists would need its DNA. But DNA disintegrates over time, meaning that after a couple of million years there is simply none of it left. Dinosaurs famously went extinct 65 million years ago, so their DNA is lost forever. No DNA, no dinosaurs.



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SHOULD WE CREATE CLONES?

FOR

According to **Angelika Schnieke**, chair of livestock biotechnology at the Technische Universitat Munchen in Germany, cloning is of immense value to biomedical science: "It has allowed us to make precise and controlled modification of animals." The applications are endless. By combining gene editing with cloning tech, we should be able to create livestock that is less susceptible to illness and disease, improving animal welfare and the livelihoods of humans to boot. Cloning also promises to give us more accurate animal models of human diseases, along with organs that can be used for transplantation. Schnieke says banning cloning would be unethical: "It makes sense if I can use fewer animals [for research]."

AGAINST

For **Helen Wallace**, director of GeneWatch UK, the creation of Dolly was a watershed moment in our relationship with the natural world, "a significant further step towards seeing animals only as commodities to be created for our convenience". The fact that cloning still remains an inefficient process is also a concern. "Cloned offspring are often aborted or die prematurely," she says. Wallace believes cloning for pets and livestock farming should not be allowed. But even when the purpose of cloning is to improve animal and human health there needs to be more scrutiny, she says: "Alternatives should be considered and non-animal testing methods developed to be widely available."

Henry Nicholls is a science writer and author. His latest book is *Sleepy Head: Neuroscience, Narcolepsy and the Search for a Good Night*.

Helen Pilcher is a science writer, performer and author of *Bring Back the King: The New Science of De-extinction*.

THE DAWN OF GM BABIES

Three-parent babies have already been born in Mexico and the Ukraine. But the birth of a child with DNA from three parents could happen for the first time this year in the UK

WORDS: **ZOE CORMIER**

Back in February 2015, Parliament voted to amend the 2008 Human Fertilisation and Embryology Act to allow 'three-parent IVF' for families that carry mitochondrial diseases. These diseases are coded in the genes and are passed from mum to child via the mitochondria, the 'batteries' of the cell.

Mitochondria are tiny disc-shaped organelles (minuscule organs) carried within cells. The primary function of mitochondria is to produce ATP, the biological currency of energy. The number of mitochondria varies widely between cell types: red blood cells don't contain any, but liver cells can hold up to 2,000 each.

Human egg cells contain mitochondria the way most cells do, but sperm cells only have them in their tails. During fertilisation, the head of the sperm, which contains its genes, is inserted into the egg. The tail of the sperm – and therefore its mitochondria – is left behind. This is why all of us only inherit our mitochrondrial DNA from our mothers.

Malfunctioning mitochondria can produce a wide variety of illnesses for which we have no cure. They regularly strike the organs that have the greatest energetic demands, including the kidneys, heart, liver, brain, muscles and central nervous system. Mitochondrial conditions are often fatal in infancy, but can frequently strike in adolescence or adulthood. It is estimated that one in 200 children in the UK carries some form of genetic mutation that could lead to mitochondrial disease at some point in life. Every year, one in 6,500 babies is born with a mitochondrial condition so severe that they will not reach adulthood – or even their first birthday.

"Mitochondrial diseases are horrible and cruel – especially because as a parent there is nothing you can do," says Liz Curtis, whose daughter Lily died at eight months old from Leigh Syndrome. While Lily died when she was young, others live for five or 10 years, slowly deteriorating. "To watch a child lose the ability to walk, talk, eat and eventually smile is crushing," says Curtis. She set up the Lily Foundation in her daughter's honour to support the families of children coping with mitochondrial conditions and to fund research into potential cures – because none were available to prevent Lily's death.

Currently in the UK, more than 150 children a year are born who will suffer severe mitochondrial disease – often unbeknown to them or their families. And new research hints that mitochondrial anomalies may play a role in the diseases of old age, such as prostate cancer and Alzheimer's. Curtis, like most parents, had no idea she carried any gene that was faulty. "I'd never even heard of mitochondrial disease, nobody in my

ILLUSTRATION: ANDY POTTS

family had. It came completely out of the blue," she says.

The main reason people like Curtis can carry a mitochondrial mutation, but not exhibit symptoms themselves, is due to a quirk of mitochondria called 'heteroplasmy'.

While the DNA in the nucleus of every single non-sex cell in the human body is identical, the selection of mitochondrial genes varies. When one cell divides, its chromosomes are duplicated; each daughter cell receives identical chromosomes. But the tiny mitochondria – remember, there can be up to 2,000 of them per cell – are split randomly between the two daughter cells. Which cell gets which mitochondria carrying which genes is a matter of chance. This is why one sibling in a family may inherit a mitochondrial disease and one will not, and why a mother can unknowingly carry a dangerous gene.

Mutations that can lead to disease are therefore scattered randomly and unevenly between different cells. Disease-causing mitochondrial mutations vary not just between individuals, but between tissue types in one person: we are all mitochondrial mosaics. A certain 'threshold' amount of a malfunctioning mitochondrial gene in any given cell needs to be reached for an illness to manifest.

ABOVE: Alana Saarinen was conceived by IVF, via a procedure that was banned by the FDA in 2001. Cytoplasm was donated from a younger donor's eggs into her mother's

BELOW: Mitochondria are the 'batteries' of cells, but also contain their own DNA

ALTERED EMBRYOS

The technique that was legalised in the UK at the beginning of 2015 allows a mother to give birth to a baby that is genetically hers, but there will not be the risk of it inheriting mitochondria with dangerous mutations. The process is known as 'mitochondrial donation' or 'mitochondrial transfer'. A mother-to-be carrying faulty mitochondria can opt to have her nuclear DNA removed from her eggs and implanted into a donor egg carrying healthy mitochondria. The egg is then fertilised with sperm from the father before being implanted into the mother's uterus for pregnancy to continue as usual.

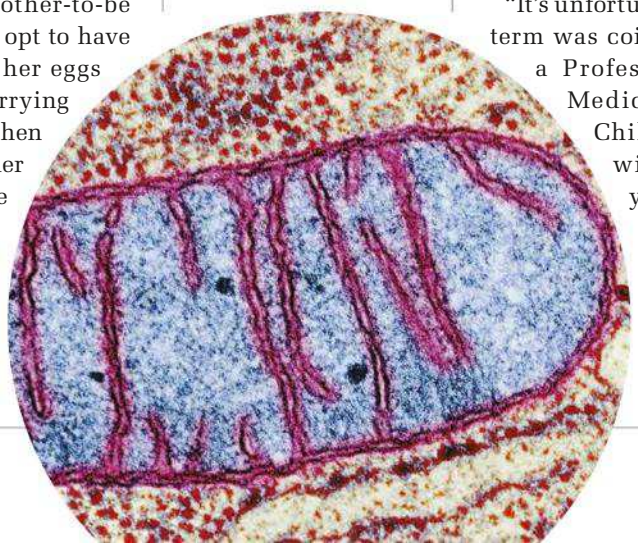
A recent study from the Wellcome Trust Centre for Mitochondrial Research at Newcastle University estimated that 2,473 women in the UK are at risk of passing a mitochondrial disease to their children and thus could benefit from the treatment.

"I'm over the moon that the law was changed. It's hugely rewarding to know that families can have their own child that will be free from disease," says Curtis.

THREE PARENTS?

Children who would be conceived in this way have been dubbed 'three-parent babies' by the press, as they technically carry DNA from three people – albeit just 37 genes from the donor egg, compared to 20,000 from the mother.

"It's unfortunate that the 'three-parent baby' term was coined," says Shamima Rahman, a Professor of Paediatric Metabolic Medicine at the UCL Institute of Child Health, who began working with mitochondrial diseases 20 years ago. "I was concerned that we were seeing a group of disorders that nobody really knew anything about, much less how to treat. They can be very debilitating and it's heartbreaking for the parents."



BRETT MOUNTAIN/POLARIS/EYEVINE, GETTY

> **“[Mitochondrial diseases] can be extremely debilitating and it’s heartbreaking for the parents”**
>
> *Shamima Rahman, Professor of Paediatric Metabolic Medicine at UCL Institute of Child Health*

Aside from sensationalism, the ‘three-parent’ nickname is misleading, in several respects. Firstly, the female mitochondrial donor is not likely to have any role whatsoever in bringing up the child. Secondly, the amount of DNA carried in the mitochondria (the 37 genes compared to the 20,000 in the nucleus) is tiny, a mere 0.1 per cent of the entire genome. And, anyway, children have already been born who carry DNA from three parents.

Women who act as surrogate mothers have been found to pass minute amounts of mitochondrial DNA to the babies they carry for nine months. Meanwhile, in the late 1990s, children conceived through ‘ooplasmic transfer’ – an IVF technique used to bolster the viability of eggs by injecting cytoplasm from young donor eggs into the older eggs of women undergoing fertility treatment – were later found to carry small amounts of DNA from the donor. Some of the resulting children are alive and well. The US Food and Drug Administration (FDA), however, put the brakes on this treatment back in 2001, and has yet to approve the new mitochondrial donation technique.

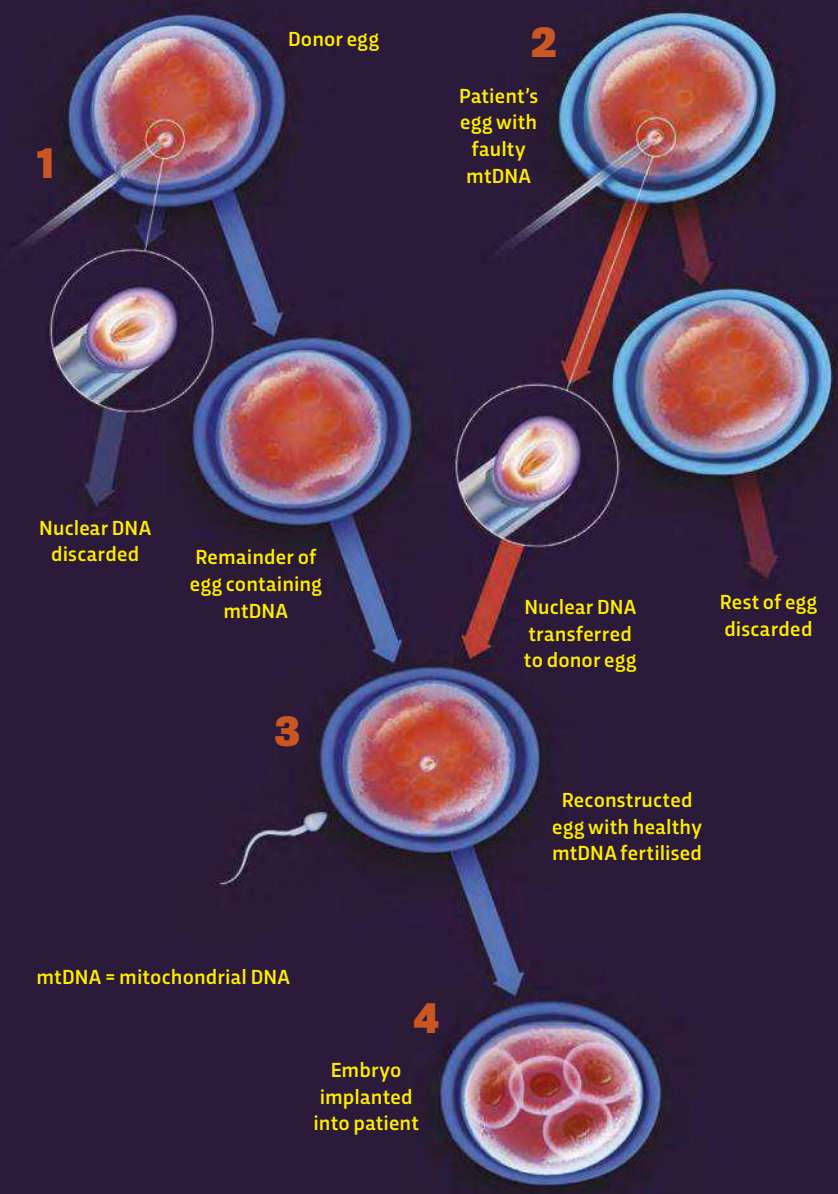
Yet mitochondrial donation is distinct from surrogacy and cytoplasmic transfer for one simple reason: it is overtly intended to create children with DNA from three parents. Thus there is something inherently more unsettling about deliberately seeking to alter the inheritable DNA of a child. Unlike a course of drug treatment, genetic changes are

ILLUSTRATION: MAGIC TORCH

HOW IT WORKS

There are several techniques for creating a baby from three parents. Here are two of them...

SPINDLE TRANSFER



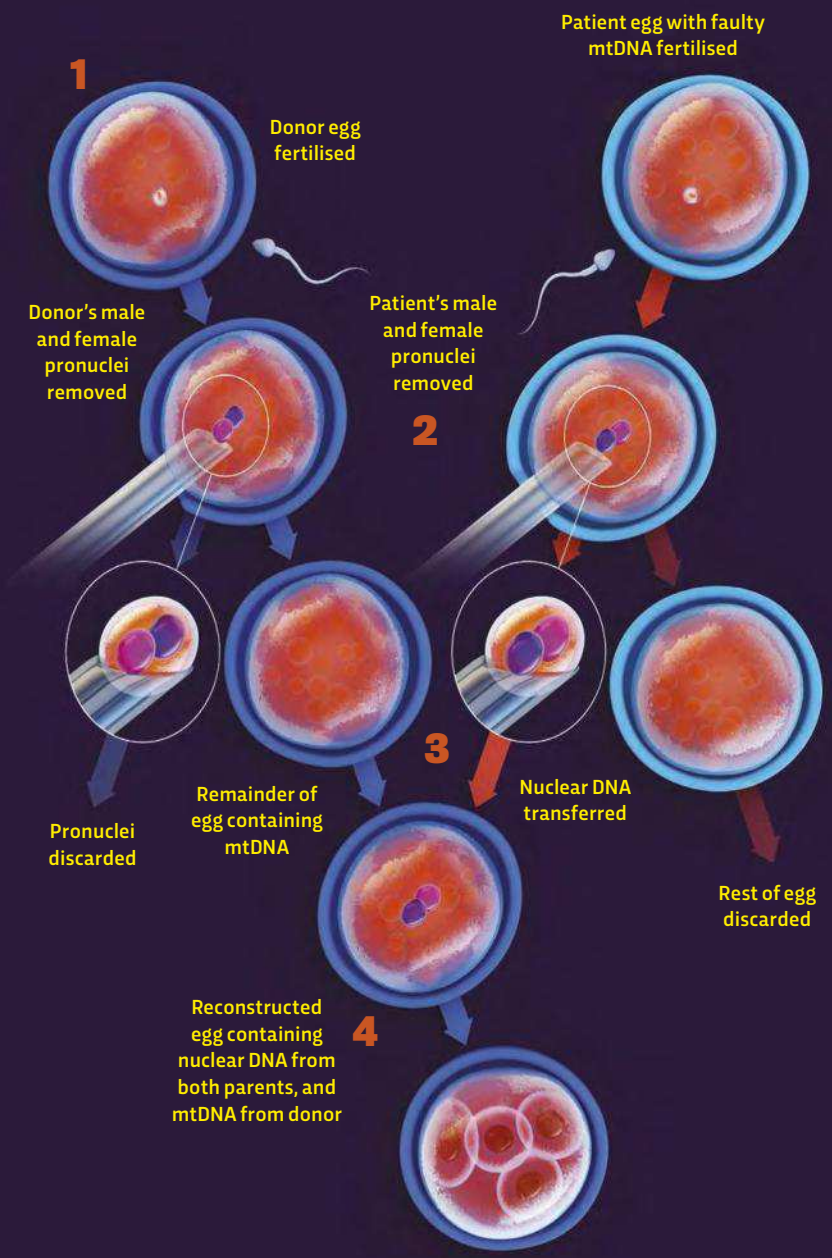
1 Start with two eggs – one from a mum-to-be with diseased mitochondria, one from a donor with healthy mitochondria. Remove nuclear DNA from both eggs.

2 Transfer nuclear DNA from the mother’s egg into the donor egg, which contains only healthy mitochondria but no nuclear DNA. Discard remainder of mother’s egg.

3 Fertilise the complete egg – now containing the mum’s nuclear DNA – with the father’s sperm. Allow to develop into an embryo.

4 Implant the embryo, now containing donor mitochondria, and DNA from both the mum and the dad – three parents in total – into the mother’s womb.

PRONUCLEAR TRANSFER



1 Start with two egg cells – one from a mum-to-be with diseased mitochondria, one from a donor with healthy mitochondria. Fertilise both with the dad's sperm.

2 Remove the pronuclei – the nuclei of the egg and the sperm, which have not yet mixed together – from both eggs. Discard the rest of the mother's egg. Discard donor's pronuclei.

3 Inject the pronuclei of the mother and the father into the donor's egg, which contains healthy mitochondria.

4 Implant embryo, which contains mitochondria from the donor, and DNA from both the mother and the father – three parents in total – into the mother's womb.

mtDNA = mitochondrial DNA

"This is world-leading science within a highly respected regulatory regime"

MP Jane Ellison, Parliamentary Under-Secretary of State for Health

permanent. *The New York Times* called the creation of these genetically modified babies "a dangerous step" and an "extreme procedure" in a 2014 opinion piece by Marcy Darnovsky, Executive Director of the Center for Genetics and Society. Naturally, this led to fears that mitochondrial donation could lead to 'designer babies' (despite the fact that mitochondrial genes do not code for visible traits such as eye colour). A Republican representative for Nebraska, Jeff Fortenberry, went so far as to call it "a macabre form of eugenic cloning".

Knee-jerk reactions aside, there are reasons to be cautious. Research is increasingly revealing that mitochondria are far more important than mere 'batteries', and have duties that include influencing the speed of nerve signalling, detoxifying ammonia in the liver, and playing a key role in programmed cell death. Moreover, genetic information is continually shuttled between the nucleus and the mitochondria. This implies that shifting mitochondria from one woman to another could have unexpected consequences down the line.

The most distressing fact about mitochondrial replacement, however, may be that it will only work for a minority of families carrying mitochondrial diseases. We now know there are 1,000 – possibly 1,500 – genes in the DNA of a nucleus that code for proteins necessary for the creation of mitochondria. Yet many of these genes can also

ILLUSTRATION: MAGIC TORCH

Could mitochondrial donation become as mainstream as IVF?

DRU DODDS

lead to faults. It is likely that only a quarter of all cases of mitochondrial disease can be attributed to genes within the mitochondria themselves. "Even from very early on, more than 20 years ago, it was clear that most of the children with mitochondrial diseases don't carry mitochondrial DNA mutations," says Rahman.

In other words, three-quarters of families carrying mitochondrial diseases somewhere in their lineage will not be able to use mitochondrial donation to protect their children. Nonetheless, the Human Fertilisation Embryology Authority carried out three scientific reviews of the treatment, and concluded that it was safe.

"It is a bold step for Parliament to take, but it is a considered and informed step," MP Jane Ellison, Parliamentary Under-Secretary of State for Health, told the House of Commons in February 2015. "This is world-leading science within a highly respected regulatory regime, and for the families affected it is a light at the end of a very dark tunnel."

Louise Brown – the first ever IVF baby – celebrates her 40th birthday this July. Back in 1978, concerns were raised about 'Frankenbabies' and 'playing God'. Today, however, more than five million children have been born via IVF. Ultimately, doctors are confident that this new technique will follow in the path of IVF to become a routine treatment that could transform lives.

Zoe Cormier is a freelance science journalist and founder of Guerilla Science.

PRE-BIRTH THERAPIES

Blood transfusions

Since 1989, foetal blood transfusions have been successfully performed. They involve injecting donor blood into a developing foetus (usually through the umbilical cord). They are used for conditions such as bare lymphocyte syndrome, an immune disorder, and severe combined immunodeficiency (SCID) or 'bubble boy syndrome'.

Stem cell transplant

Blood transfusions are usually given to patients only once symptoms of diseases appear. But to treat inherited conditions such as SCID and sickle cell anaemia much earlier, researchers are trialling treatments that involve injecting donor stem cells into a foetus. No human trials have taken place yet but animal studies are promising.

Prenatal gene therapy

Gene therapies, which use modified viruses to deliver genes into a patient's nuclear DNA, have been used for over 20 years to treat adults and children with certain diseases. But for many conditions, such as cystic fibrosis, organ damage has already taken place by childhood – sometimes even before birth. By treating foetuses in the womb, researchers hope to stop damage before it starts. There have been successful trials in mice, monkeys and sheep.

Foetal 'priming'

Researchers are exploring the potential to 'prime' the immune systems of developing foetuses by transplanting proteins (rather than genes or entire cells). Adults with haemophilia can be treated with injections of blood clotting proteins, but about one-fifth of people reject the donor proteins. By 'priming' the immune systems of foetal mice with umbilical cord injections of the protein, the baby mice were more likely to accept transplants after birth.

GM FOOD SOMETHING TO CHEW OVER

GM FOOD HAS BEEN AROUND FOR OVER 30 YEARS, YET IT STILL IGNITES HEATED DEBATE. SO IS IT SAFE, AND SHOULD WE ALLOW IT TO GRACE OUR SHELVES IN THE FUTURE?

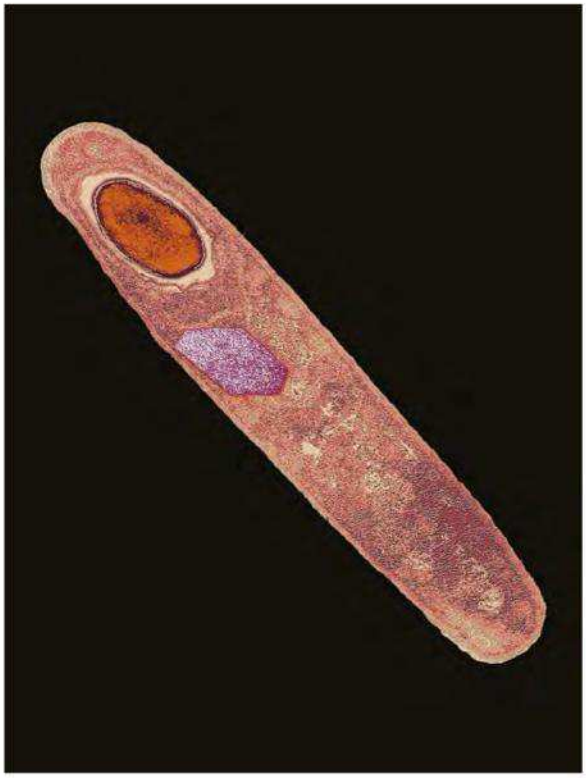
WORDS: **JIM DUNWELL**

GETTY

ABOVE: A researcher in Minnesota attends to an experimental crop of GM corn

RIGHT: Genes from this soil bacterium, *Bacillus thuringiensis*, can be inserted into crops to make them resistant to certain insect pests

FAR RIGHT: Different genetically modified strains of soybean are being grown in this field in Iowa



GETTY, SCIENCE PHOTO LIBRARY X2

For most people, Miami is either a sun-drenched holiday destination or the favoured location for US crime dramas. However, in 1983, it was forever written in the annals of science as the place where it was first announced that we could introduce specific genes into plant cells, then generate whole plants with only a single altered characteristic. Before that, plant breeders had been confined to crossing together two parents and then screening the resulting plants for that rare individual that emerged with better properties. This process was by its nature hit and miss and it took several years before a new variety with the desired properties could be bred. Suddenly it became possible to make specific alterations to an existing variety with relative ease. Thus began the age of genetically modified (GM) or transgenic agriculture.

From that point onwards a race began, headed by US agricultural and agrochemical company Monsanto, to exploit this tech and develop novel varieties of crops. The first targets were those predicted to generate the largest sales. The two dominant products were plants designed to be tolerant to herbicides – particularly the Monsanto product glycophosate – so weeds could be killed without harming crops, and those expressing toxin-encoding genes from the soil bacterium *Bacillus thuringiensis* (Bt) to give them resistance to certain insect pests. The strategy behind these approaches represented something of a revolution. In the period straight after WWII, research investment focused solely on the discovery of new herbicides and insecticides. But now, scientists could achieve the same effect by modifying genes within the crops rather than inventing new chemicals to spray on them. The first GM crops came to the US market in 1996 and sales grew rapidly.

It is estimated that sales of GM seed in 2015 amounted to $15.3bn. This was grown in over 20 countries on an area greater than 440 million acres – more than a 100-fold increase since 1996. In 2015, the top five countries in order of area of GM crops cultivated were the US (175 million acres), Brazil, Argentina, India and Canada. In the US, more than 90 per cent of all maize, soybean and cotton is GM, while only about 290,000 acres were grown in the EU (mostly in Spain) – all were an insect-resistant variety of maize.

Although GM seed is more expensive, the cost can be seen as an insurance policy against crop losses due to weeds and pests

Although GM seed is more expensive than conventional equivalents, the extra cost can be seen as an insurance policy against crop losses due to weeds or pests. No longer is it necessary to spend so much time and money on the application of repeated sprays of herbicides or insecticides.

So why have EU farmers not taken the same route? The answers are based on differences in both the supply of GM seed and the demand for it. First, the range of crops differs between the two regions, with very little soybean being grown in Europe. Perhaps more importantly, attitudes to GM crops and to food derived from such crops are different on the two sides of the Atlantic. In the US, agriculture takes place mainly in regions that are far removed from the main centres of population, and who also have a general acceptance of government policy to GM.

In Europe, however, there is much greater awareness of farming locations as people tend to live closer to agricultural areas. In many countries, there is also a greater distrust of government and the regulations surrounding GM. But these views are not held uniformly across Europe. Such diversity, allied to the complex politics within the present 28 EU member states, means that few GM crops have even been approved for cultivation. This has led to the withdrawal of commercial investment in GM in Europe, to be redirected to the US or Southeast Asia. This continues the trend of rapid commercial consolidation, to potentially just three massive conglomerates in the future – a significant issue to many who see commercial domination of agriculture, including GM, as detrimental to fair competition and a threat to livelihoods in the developing world.

ARE GM FOODS SAFE?

In addition to opposition based on the perceived danger of concentrating commercial power in fewer hands, there is also vocal criticism of GM on the grounds of food and environmental safety. But is there any evidence of this? First, it is helpful to consider the origin of the crops that we eat. Many farmed crops are genetic mutations of their wild ancestors, with such spontaneous mutations having been identified as occuring between 10,000 and 20,000 years ago, when humans moved from hunting and gathering to farming. These mutations led to dramatic changes in characteristics. For example, wild species of potato often contain toxic levels of chemicals called glycoalkaloids – compounds that protect them from insect attack. Similarly, the amount of edible fruit in a wild tomato is much smaller than in their farmed counterparts.

GM protesters outside the EU headquarters in Brussels

GETTY X2

Over the last 20 years there has been no confirmed harm to the millions of humans that have eaten GM food

Our recent ability to sequence the DNA of crops has led to interesting findings about these evolutionary processes. It is now clear that genomes have continually been gaining and losing genes. The gains have often come from other species, as part of a process known as 'horizontal gene transfer'. Humans, for example, contain approximately 50 genes transferred from other organisms, including 27 genes from a diverse range of viruses. We should therefore consider the genomes of organisms not to be fixed, but subject to gradual change.

But do any of these genetic changes, whether naturally induced or brought about by humans, have an impact on food safety? Every part of our body, from skin to bones, and from blood to brain, is composed of chemical constituents obtained by the breakdown and reassembly of food. The DNA and proteins in food from GM crops have exactly the same chemical building blocks as those found in any other food. Over the last 20 years there has been no confirmed harm to the millions of humans that have eaten GM food, whether as fresh fruit such as papaya, or as processed products from maize, soy, sugar beet or oilseed rape.

In fact, the main global food safety

Farmers have been selectively breeding crops for centuries: carrots used to be purple in colour, but were bred to the more familiar orange – and all without genetic modification

issue is with food-borne diseases caused by contamination, principally with bacteria such as Salmonella and *E. coli*, viruses, parasites, toxins and chemicals. In 2015, the World Health Organization (WHO) produced the first ever estimates of the global burden of foodborne diseases, and showed almost 1 in 10 people fall ill every year from eating contaminated food and 420,000 die as a result. This also has a significant economic impact. Germany's 2011 *E. coli* outbreak, which caused 50 deaths after consumption of sprouted organic fenugreek seed, reportedly led to $1.3bn in losses for farmers and industries and $236m in emergency aid payments to 22 European Union member states.

Some people are concerned about the potential danger posed by the spread of introduced genes from GM crops to their wild relatives. Such 'genetic pollution' is seen as irreversible and a threat to species diversity or stability. Although the gene that codes for herbicide resistance has been shown to transfer in the pollen of a GM grass to a wild relative, this has no environmental consequence. Also, a low frequency of pollination is known to occur between cultivated crops and their wild relatives and vice versa.

In most industrialised countries, and in many parts of the developing world, there are government regulations that cover the import and cultivation of GM crops, and guidance on whether or not the food derived from GM crops has to be labelled. In the EU and US, the regulation applies to the process by which a GM organism is produced. In contrast, regulation in Canada focuses on the product generated, not the method by which it was produced. Many scientists around the world now think the logical target of regulation should be the product and not the process, because this approach could accommodate all the new breeding tech that have been developed in recent years.

THE FUTURE OF GM

We have the somewhat contradictory situation in Europe that only a tiny area of farmland is used for cultivating GM crops, yet about 90 per cent of imported soybeans – a major constituent of animal feed – come from GM sources. This means that people in the EU indirectly consume a large amount of GM because many animals eat imported GM feed. Meat, milk and eggs from animals fed on these products are sold throughout the UK, but do not need to be labelled as GM. In contrast, products for direct human consumption are labelled as containing GM ingredients. In the US, however, once a product has received regulatory approval it is considered equivalent to that from a non-GM source and doesn't need to be labelled.

Several economic studies have shown that removing GMOs from the foodchain would have a significant impact. One carried out at

Cows in Europe are often fed on GM soybeans, meaning that when people eat beef or drink milk they are indirectly (and perhaps unknowingly) consuming GMOs

GETTY, SCIENCE PHOTO LIBRARY

Meat, milk and eggs from animals fed on GM products are sold in the UK. Such products do not need to be labelled

Rather than relying on selective breeding, scientists can use gene editing to create crops with particular traits

Purdue University in the US in 2016 found that if GMOs were eliminated, there would be lower crop yields and commodity prices would rise. Corn (maize) prices would increase by as much as 28 per cent and soybeans by up to 22 per cent. In real terms, shoppers could expect their food prices to rise up to 2 per cent.

A similar study carried out at North Carolina State University in 2015 found that if someone in the US wanted to convert to a GM-free diet, then when directly compared item by item, GM-free food costs an average of 33 per cent more than a comparable food item that is not GM-free. When compared on a per-ounce basis, GM-free foods cost an average of 73 per cent more. Generalising to the cost of a typical basket of food consumed by US households, the consumption of GM-free food would increase the average family food budget from $9,462 to $12,181 per year.

So what is the status of GM technology now that it is approaching middle age? Will it soon die out? Or will it flourish further and help to contribute towards feeding future billions? Based on objective evidence, the great majority of international scientists deem the tech to be safe, while also acknowledging that some parties may have socioeconomic and/or ethical grounds for opposition. Regardless, research continues apace. There are dozens of new forms of GM and gene-edited crops, and a few animals, currently being developed. These include non-browning apples and potatoes, purple tomatoes packed with extra nutrients, and even the AquaBounty salmon – a fish genetically modified to grow throughout the year, making it cheaper to produce and lessening its environmental impact.

These products will possibly have more direct benefit to the consumer than the previous products aimed primarily at the farming industry. In the UK, it is possible that new legislation will encourage a more logical and proportionate regulatory system that might allow the scientific talent in this country to be used more effectively. But only time will tell whether this happens and GM technology leaves a legacy in the form of another generation of science.

BBC RADIO 4

Listen to *The Inquiry* discussing whether our opposition to GM crops is irrational
bbc.in/1eNuEsd

Jim Dunwell is a professor of plant biotechnology at the University of Reading. He researches plant breeding, gene expression and protein evolution.

BIOHACK

Amateurs are altering DNA as a hobby. So who are they and what are they up to?

WORDS: **JV CHAMARY**

Although many of us think 'hacker' means a person who breaks things (technically, that's a 'cracker'), the word more properly applies to people who make or repurpose things, especially those who tinker with technology. 'Biohackers' play with biotechnology and form part of the fairly new Do-It-Yourself biology movement.

DIY bio groups are for amateurs – not professional scientists – and are run by volunteers. Members usually pay a monthly fee to cover the costs of facilities and supplies for a shared lab, which provides affordable access to anyone curious about biology.

In 2010, there were only a few biohacking labs. But, according to diybio.org, there are now over 60 local groups around the world. In 2015, the UK Health and Safety Executive (HSE) registered London-based Biohackspace as 'GM Centre 3266' – the first lab in the country that allowed anyone to try their hand at genetic engineering.

Groups generally start out as 'garage biology' – just like in the early days of modern computing where mavericks such as Steve Jobs, Steve Wozniak and Bill Gates developed operating systems in a garage. But the groups then often grow into something larger. BioCurious in California is an enterprising hackspace bringing DIY bio to Silicon Valley. Since opening over eight years ago, BioCurious has welcomed everyone from entrepreneurs developing proof-of-concept products to high-school students working on their science fair projects. The group grows by two or three members every month, and currently includes anthropologists, physicists and software engineers.

One BioCurious community project on bioluminescence was spun-out as Glowing Plant, which raised $485,000 on Kickstarter. Glowing Plant's former lead scientist, Dr Kyle Taylor, now runs a 'plant research group' at BioCurious, where 15 members work on half a dozen projects.

Back across the Atlantic, one of Biohackspace's collaborations involved making 'kombucha pancakes'. Kombucha is produced by a colony of microbes, the most important being *Gluconacetobacter*, which secretes strands of cellulose. Unlike material made by plants, a kombucha pancake is almost pure cellulose. When thin, it can be dried for paper, and used in wound dressings and high-end speaker cones. When thick, it's tough enough for clothing – a sort of vegan leather.

Groups start out as 'garage biology' – just like in the early days of modern computing with Jobs and Wozniak

Another project exploited the trend for home brewing in the form of a 'DIY Beer Kit'. The kit includes a pick-and-mix of yeast strains, each

JV CHAMARY

KERS

CLOCKWISE FROM TOP: Prototype cell-washing to remove salt so bacteria accept new DNA; Before being dried, kombucha is a gooey, rubbery substance; Biohackspace lab members discussing future plans

By genetically engineering these silkworms, using the CRISPR Cas-9 system, the creatures can fight off lethal viruses

GETTY

> "Informally, I'm not sure how many times the FBI may have dropped in"

genetically modified to make molecules that offer weird and wonderful flavours. Biohackspace entered its DIY Brew Kit in the 2015 International Genetically Engineered Machine (iGEM) competition, where it won a bronze medal.

DIY bio and iGEM are closely linked to synthetic biology, which involves building living machines from a set of standard parts – 'genetic Lego blocks' called BioBricks. This requires a toolkit, and the most powerful new technique in molecular biology is the CRISPR-Cas9 system, known as 'CRISPR'.

CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats) are sequences of DNA letters, first discovered in *E. coli* in 1987. A decade later, researchers revealed that CRISPRs form part of an anti-viral defence system used by bacteria and other microbes: after a virus invades a cell, enzymes cut and paste bits of the viral genome between CRISPR sequences in the cell's DNA. This leaves a genetic memory for an RNA 'guide' that an enzyme called 'Cas9' uses to recognise and destroy viral DNA, should an invader return. In 2012, bioengineers showed that the RNA guide could be reprogrammed to target any DNA sequence.

Unlike most gene-editing techniques, CRISPR is revolutionary because the technology is precise. It's also quick, cheap and easy to use – so simple that even amateurs can use it.

PLAYING SAFE

Anyone who tinkers with nature can be accused of 'playing God'. And given that some people are wary of genetic modification by professional scientists, it's understandable that some might worry about amateurs meddling with organisms they don't understand.

But even with CRISPR, we shouldn't overestimate what biohackers are capable of. "CRISPR is merely a tool – you still have to have an idea of what genes you want to turn on and off," explains Dr Darren Nesbeth, a synthetic biologist at UCL. "Knowledge itself is the biggest barrier to being able to redesign a cell."

Biohacking is also limited by the resources available to a typical DIY bio lab. Reagents such as enzymes can be expensive, and companies that manufacture CRISPR sequences have safeguards to ensure they don't supply potentially malicious genetic material. "Somebody can't order the sequence to build the Ebola virus," says Maria Chavez, Executive Director, Treasurer & Director of Community Engagement at BioCurious. "Nobody is going to sell you those genes."

Objections to biohacking are similar to arguments in the GM debate, which discuss hypothetical scenarios such as strains escaping, or terrorists designing weapons. Nonetheless, DIY bio groups take it seriously. US government agencies like the FBI and Department of Defense keep in touch and send agents to visit labs. "At the beginning they were coming through quite frequently – at least once a month, formally," says Chavez. "Informally, I'm not sure how many times they may have dropped in."

DIY bio groups also have rules for what their members can work with. Nesbeth says: "There's a framework and guidance equivalent to what happens at a university."

Dr JV Chamary is a biologist and writer. His latest book is *50 Biology Ideas You Really Need To Know.*

BBC RADIO 4

Listen to an episode of *FutureProofing* on how easy it is to become a biohacker
bbc.in/1KSRnRj

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Each life form on this planet has a unique genetic code – DNA – whose structure was first identified 65 years ago. Now geneticists are using DNA to improve our health, eliminate hunger and even bring back animals from the dead. In this special issue, experts explain the basics of genetics, reveal the gene therapies to help us live longer, and explore the future of genetics from cloning to designer babies.

FROM THE MAKERS OF ***BBC FOCUS*** MAGAZINE